BCG Vaccination
(Papers)

Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1972, 46, 371-385

BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life

FOURTH REPORT TO THE MEDICAL RESEARCH COUNCIL BY ITS TUBERCULOSIS VACCINES CLINICAL TRIALS COMMITTEE *

This paper reports the 15-year results of a controlled clinical trial of BCG and vole bacillus vaccines in the prevention of TB. Among 54 239 participants, 583 cases of TB developed, of which 70 % were of pulmonary TB and 15 % of tuberculous pleural effusion without evidence of pulmonary TB. The annual incidence (per 1 000) of TB was 0.28 among the 13 598 BCG-vaccinated participants and 1.28 among the tuberculin-negative unvaccinated participants admitted concurrently (a 78 % reduction); for vole bacillus vaccine (5 817 participants) the figures were 0.29 and 1.50 (an 81 % reduction). Protection extended to all forms of TB (in particular, 10 cases of tuberculous meningitis or miliary pulmonary TB developed in unvaccinated, and none in vaccinated, participants) and was similar in the two sexes. It decreased gradually during the period but was still substantial (59 % for BCG vaccine and 73 % for vole bacillus vaccine) 10–15 years after vaccination; no definite conclusion can yet be reached on the level of protection after 15 years. The annual incidence of TB in those with strong positive reactions to tuberculin on entry was particularly high (3.75) in the first 2.5 years, reflecting active infections acquired before entry; those with weaker positive reactions on entry had a lower incidence throughout than the tuberculin-negative unvaccinated group, indicating that a degree of naturally acquired immunity (though less than that conferred by vaccination) was associated with the low-grade tuberculin sensitivity. The incidence of every form of TB decreased steeply during the 15 years, except for genito-urinary TB of which there were 3, 5, and 14 cases in successive 5-year periods, principally among initially tuberculin-positive participants. This report also presents the findings with respect to nontuberculous diseases, discusses the place of vole bacillus vaccination, and describes a method for assessing the applicability of mass BCG vaccination in a given epidemiological situation.

A controlled clinical trial of the effects of BCG and vole bacillus vaccines during adolescence and early adult life was started in England in 1950. More than 50 000 children of both sexes participated, nearly all aged 14 to 15½ years on entry, initially free f... both active tuberculosis and known contact w.... the disease at home, and originally living in urban or suburban areas in or near north London, Birmingham, and Manchester. Those with negative reactions to tuberculin on entry were vaccinated with BCG or vole bacillus vaccine, or left unvaccinated, according to a method of random allocation. All the participants, including those with positive reactions to tuberculin initially, were followed up to discover the cases of tuberculosis occurring among them.

The three reports already published (Great Britain, Medical Research Council, 1956, 1959, 1963) gave further details of the trial and showed that the two vaccines conferred substantial protection against tuberculosis for up to nearly 9 years after vaccination. This report summarizes the results after each participant had been in the trial for 15 years, and reviews the trial and its findings.

NUMBER OF PARTICIPANTS

Of the 58 314 children who presented themselves during 1950–52 for the first examination, 4 075 have been excluded for reasons given in the third report (Great Britain, Medical Research Council, 1963), leaving 54 239 for analysis. According to the tuberculin tests and vaccinations given at the first

* See page 383.

examination, the 54 239 children were automatically classified at the outset into the following five groups:

Negative to 100 tuberculin units (TU), left unvaccinated	12 867
Negative to 100 TU, vaccinated with BCG	13 598
Negative to 100 TU, vaccinated with vole bacillus	5 817
Positive to 3 TU [1]	15 704
Negative to 3 TU, positive to 100 TU	6 253

The result of a tuberculin test was classed as negative if the test produced no palpable induration or an induration whose greatest diameter measured less than 5 mm at 72 hours, and as positive if the induration measured 5 mm or more. Previous reports (Great Britain, Medical Research Council, 1956, 1959) have described in detail the scheme according to which negative reactors to 100 TU were randomly allocated to the vaccinated or unvaccinated groups. The major reason for the differing numbers in the first three trial groups is that vole bacillus vaccine was not used in all the trial areas.

METHODS OF FOLLOW-UP

The methods of follow-up of participants have varied during the 15-year period. Until September 1960—i.e., for nearly 9 years on the average—the basic method consisted in a cycle of intensive inquiry and examination by MRC teams, repeated at intervals of about 14 months, with (*a*) an inquiry form by post; (*b*) a home visit by a trained nurse about 6 months after the postal inquiry; and (*c*) a chest radiograph and tuberculin test about 4 months after the home visit. Those who moved to another area of the country, or who emigrated, were followed up individually in the same way by the local health authority (Great Britain, Medical Research Council, 1959). Where appropriate, arrangements were also made with the armed services for the close follow-up of participants during their 2-year period of national service (Great Britain, Medical Research Council, 1959).

In addition to these individual approaches to each participant, the teams were provided with information from the records of the chest clinics in the districts concerned and from the tuberculosis notification lists of the local medical officers of health. Cases of tuberculosis were therefore discovered both by the periodic MRC radiographic examinations and by the normal methods of the National Health Service.

In September 1960 the periodic MRC radiographic examinations were discontinued, but contact with individual participants was maintained through annual postal inquiries. In addition, the scheme for obtaining information regularly on persons in the appropriate age groups who had, or were suspected of having, tuberculosis were extended outside the trial districts to include all chest clinics and medical officers of health throughout Great Britain. Cases of tuberculosis detected by the National Health Service among all participants still resident in the country have thus continued to be reported direct to the MRC Tuberculosis and Chest Diseases Unit.

Experience since 1960 showed that few of the cases of tuberculosis among the participants who lived in Great Britain escaped the statutory notification system and did not come to the notice of a chest clinic, but were detected only by the postal inquiry. These exceptions were all cases of non-pulmonary tuberculosis and amounted to about one per year. For the years 1966 and 1967, therefore, a scheme for obtaining information on cases in which non-pulmonary tuberculosis was present or suspected, similar to the arrangements for chest clinics and medical officers of health, was operated in hospitals in the original trial areas. However, this scheme yielded no cases that were not detected by other means. Following a special effort to establish postal contact with every participant after he or she had been in the trial for 15 years, the postal inquiries were stopped finally at the end of 1967. However, the arrangements for obtaining information through chest clinics and medical officers of health were continued and have disclosed a few additional cases of tuberculosis that started within 15 years of entry to the trial.

ASSESSMENT OF CASES

The case records of all patients with tuberculosis or suspected tuberculosis, or with any other pulmonary radiographic abnormality persisting for more than 14 days, that came to the notice of the Tuberculosis and Chest Diseases Unit as a result of these follow-up procedures, were submitted for classification to an independent assessor who was kept unaware of the results of any tuberculin tests and whether or not vaccination had been performed.

[1] The 3-TU dose of Old Tuberculin is approximately equivalent to a dose of 0.00002 mg (1 TU) of RT 23 in a buffer containing Tween 80 (the current WHO standard tuberculin test).

The assessment was made from the series of radiographs and the findings of all the clinical and other examinations of the patient, both on diagnosis and subsequently. Unfortunately, as explained previously (Great Britain, Medical Research Council, 1956, 1959), no special emphasis was laid, in the early 1950s, on intensive bacteriological examinations in the routine management of many of these cases at local chest clinics. It would therefore have been unrealistic and misleading to classify the cases as tuberculous or nontuberculous on bacteriological findings alone, although this is now the recommended practice (WHO Expert Committee on Tuberculosis, 1964).

INCIDENCE OF TUBERCULOSIS

A total of 583 cases of tuberculosis, all of which began within 15 years of entry to the trial, were discovered. Of these, 243 occurred in the tuberculin-negative unvaccinated group, 56 in the BCG-vaccinated group, 25 in the group vaccinated with vole bacillus, 206 among those who initially had positive reactions to 3 TU, and 53 among who initially had positive reactions only to 100 TU.

As in the earlier reports, the value of BCG vaccination has been judged from the experience of participants admitted concurrently to the different trial groups (Table 1, section A). There were 240 cases of tuberculosis among 12 699 tuberculin-negative unvaccinated participants, representing an annual incidence of 1.28 cases per 1 000 (allowing for persons who died or contracted tuberculosis and thus ceased to be at risk of the disease). Among the 13 598 BCG-vaccinated participants admitted concurrently with them there were 56 cases, the annual incidence being 0.28 per 1 000. Thus the reduction in incidence was 78.4%, and the possibility that this difference occurred by chance is remote (less than one in a million). Among the participants who initially had positive reactions to 3 TU the annual incidence was 0.89 per 1 000 and among those who had positive reactions only to 100 TU it was 0.57 per 1 000, these rates lying between the rates for the tuberculin-negative unvaccinated and BCG-vaccinated groups.

Section B of Table 1 gives corresponding information for the smaller number of subjects who received vole bacillus vaccine and for those admitted con-

Table 1. Cases of tuberculosis starting within 15 years

Section [a]	Trial group	Number of participants	Cases of tuberculosis		Protective efficacy (%)
			Number starting within 15 years	Annual incidence per 1 000 participants [b]	
A	Children given BCG vaccine and those admitted concurrently with them	Negative, unvaccinated	12 699	240	1.28	
		Negative, BCG-vaccinated	13 598	56	0.28	78.4
		Positive to 3 TU	15 514	204	0.89	
		Positive only to 100 TU	6 153	52	0.57	
B	Children given vole bacillus vaccine and those admitted concurrently with them	Negative, unvaccinated	5 889	130	1.50	
		Negative, vaccinated with vole bacillus	5 817	25	0.29	80.8
		Positive to 3 TU	8 783	118	0.91	
		Positive only to 100 TU	3 068	32	0.70	
C	Children admitted concurrently and given either BCG or vole bacillus vaccine	Negative, BCG-vaccinated	5 581	17	0.20	
		Negative, vaccinated with vole bacillus	5 497	21	0.26	

[a] Many participants and cases of tuberculosis appear in more than one of the three separate sections of this table (see text) and the figures from different sections can therefore not be totalled. The total cases in each trial group are shown in Table 2 and the total numbers of participants in Table 3.

[b] After allowing for removals from the population at risk, i.e., by death or by contracting tuberculosis.

currently to the tuberculin-negative unvaccinated and the tuberculin-positive groups (this comparison includes some, but not all, of the children considered in section A). There were 130 cases among 5 889 tuberculin-negative unvaccinated participants (1.50 per 1 000 annually) and 25 among the 5 817 who were vaccinated with vole bacillus (0.29 per 1 000 annually). The reduction in incidence was 80.8%. Again, the possibility that this difference occurred by chance is less than one in a million. The annual incidence was 0.91 per 1 000 among participants who had positive reactions to 3 TU and 0.70 per 1 000 among those who had positive reactions only to 100 TU, these rates lying between the rates for the tuberculin-negative unvaccinated group and those vaccinated with vole bacillus.

Finally, section C of Table 1 provides a comparison of BCG and vole bacillus vaccination, based on the concurrent admissions to these two groups (all of which are included in section A or section B). The annual rates for these two groups were similar—i.e., 0.20 per 1 000 for those who were vaccinated with BCG and 0.26 per 1 000 for those who received vole bacillus vaccine.

It is evident that the incidence of tuberculosis in the corresponding trial groups of the different sections of Table 1 was similar. Consequently it is unnecessary to set out the further results in this report on a strictly concurrent basis; instead, they are presented for the whole of each trial group.

THE FORMS OF TUBERCULOSIS

The forms of tuberculosis that occurred in each trial group are shown in Table 2. Of the total of 583 cases in all the groups combined, 406 (70%) were of non-miliary pulmonary tuberculosis. There was little variation between the five trial groups in the ratio of pulmonary tuberculosis cases to the total number of cases.

Tuberculous pleural effusion without pulmonary tuberculosis was the next most common form, with 85 cases (15% of the total). The other two common forms of the disease were tuberculous adenitis (28 cases—5%) and genitourinary tuberculosis (22 cases—4%). Most of the cases in these two categories developed among participants who initially had positive reactions to 3 TU; tuberculous adenitis accounted for 22 (11%) and genitourinary tuberculosis for 16 (8%) of all the cases in this trial group. There were 14 cases of tuberculosis of the bones and joints, of which 6 occurred in participants who initially had positive reactions to 3 TU.

Table 2. Cases of tuberculosis starting within 15 years, according to the form of the disease

Trial group	Total cases	Form of tuberculosis											
		Pulmonary tuberculosis, non-miliary		Tuberculous pleural effusion [a]	Hilar gland enlargement [b]	Tuberculous meningitis	Pulmonary tuberculosis, miliary	Bone or joint tuberculosis	Tuberculous adenitis	Tuberculous peritonitis	Erythema nodosum	Genitourinary tuberculosis	Other forms [c]
		No.	%										
Negative, unvaccinated	243	163	67	51	2	5	5	3	4	2	4	3	1
Negative, BCG-vaccinated	56	40	71	8	1	0	0	2	1	1	1	2	0
Negative, vaccinated with vole bacillus	25	20	80	4	0	0	0	1	0	0	0	0	0
Positive to 3 TU	206	143	69	14	0	1	1	6	22	1	0	16	2
Positive only to 100 TU	53	40	75	8	0	0	0	2	1	1	0	1	0

There were 6 cases of tuberculous meningitis—5 in the tuberculin-negative unvaccinated group and 1 among those who initially had positive reactions to 3 TU. In addition, 6 cases of miliary pulmonary tuberculosis occurred—5 in the tuberculin-negative unvaccinated group and 1 among those who initially had positive reactions to 3 TU.

EXTENT AND NATURE OF THE PULMONARY LESIONS

In earlier reports (Great Britain, Medical Research Council, 1959, 1963) the extent of the pulmonary lesions and the presence of cavitation on the first abnormal chest radiograph were analysed as indicators of the relative severity of the cases in the vaccinated and tuberculin-negative unvaccinated groups. It was noted that pulmonary lesions among those vaccinated were slightly (but not significantly) less extensive when first detected than those occurring in the tuberculin-negative unvaccinated group.

However, the extent of pulmonary disease at the time when it can be diagnosed by means of a chest radiograph—whether this is made routinely or on account of symptoms—is not necessarily a precise indicator of the severity of the whole tuberculous disease process. Furthermore, the early use of chemotherapy in the great majority of these cases precluded any useful later assessment of their severity. The evidence on severity of disease from the earlier analyses must therefore be regarded as being of doubtful value. Corresponding analysis of all cases that occurred within 15 years of entry (not tabulated here) shows no significant differences between the vaccinated and tuberculin-negative unvaccinated groups as regards the initial extent of pulmonary lesions or presence of cavitation.

INCIDENCE OF TUBERCULOSIS IN THE TWO SEXES

There were 277 cases of tuberculosis among the 28 230 male participants, and 306 among the 26 009 females, in all the trial groups combined. The incidence among females was 20% greater than among males. A similar excess was found in each of the trial groups separately throughout the 15 years (the figures have not been tabulated here).

The reduction in incidence in the BCG-vaccinated group, compared with the tuberculin-negative unvaccinated group, was 82% for males and 74% for females—a non-significant difference. The corresponding figures for those vaccinated with vole bacillus were 79% and 75%, respectively—also a non-significant difference.

INCIDENCE OF TUBERCULOSIS IN DIFFERENT PERIODS SINCE ENTRY TO THE TRIAL

The date of the earliest radiographic or (for non-pulmonary disease) the earliest clinical manifestation of tuberculosis has been regarded as the starting point of the disease. Table 3 shows the cases

Table 3. Cases of tuberculosis, according to the interval between entry and the earliest radiographic or clinical manifestation (the starting point) of the disease [a]

Trial group	Number of participants	Cases of tuberculosis						Annual incidence per 1 000 participants [b]				
		Interval in years						Interval in years				
		0–	2 ½–	5–	7 ½–	10–	12 ½–15	0–	2 ½–	5–	7 ½–	10–15
Negative, unvaccinated	12 867	68	92	41	26	11	5	2.12	2.89	1.30	0.83	0.26
Negative, BCG-vaccinated	13 598	14	13	13	9	2	5	0.41	0.38	0.38	0.27	0.10
Negative, vaccinated with vole bacillus	5 817	7	5	6	5	1	1	0.48	0.34	0.41	0.35	0.07
Positive to 3 TU:												
induration of 15 mm or more	6 866	64	31	17	7	11	5	3.75	1.83	1.01	0.42	0.48
induration of 5–14 mm	8 838	17	19	12	7	9	7	0.77	0.86	0.55	0.32	0.37
Positive only to 100 TU	6 253	12	19	9	6	1	6	0.77	1.22	0.58	0.39	0.23
All groups	54 239	182	179	98	60	35	29	—	—	—	—	—

[a] Some of these figures differ slightly from those given in the previous reports (Great Britain, Medical Research Council, 1956; 1959, 1963) as a result of more recent information.

[b] After allowing for removals from the population at risk, i.e., by death or by contracting tuberculosis.

starting in successive 2½-year periods since entry to the trial, together with corresponding incidence figures; Table 4 gives assessments of the protective efficacy (in %) of the BCG and vole bacillus vaccines in successive periods. In calculating the incidences and the percentage protection, the cases occurring during the period 10–15 years have been combined because the numbers are small.

The average incidences during the 15-year period of the trial, presented in an earlier section, conceal substantial variations in the incidence of tuberculosis with time in all five trial groups. In Table 3 those who initially had positive reactions to 3 TU have been subdivided into persons with an induration of 15 mm or more and those with a 5–14-mm induration, because the experience of these subgroups differed (Great Britain, Medical Research Council, 1956, 1959).

In the tuberculin-negative unvaccinated group the annual incidence was 2.12 per 1 000 during the first 2½ years and rose to 2.59 per 1 000 during the next 2½ years. It then fell steeply to 1.30, then to 0.83 and, between 10 and 15 years, to 0.26 per 1 000. In the BCG-vaccinated and in those vaccinated with vole bacillus, the annual incidences during the first 2½ years were 0.41 and 0.48 per 1 000, respectively. In each group the incidence showed a gradual downward tendency in successive periods up to 10 years, followed by a substantial decrease between 10 and 15 years; during this period the incidences were 0.10 and 0.07 per 1 000, respectively.

As a result of these trends, the percentage reductions in incidence in the BCG-vaccinated group, compared with the tuberculin-negative unvaccinated group, were 81, 87, 70, 68, and (between 10 and 15 years) 59% in successive periods (Table 4). The corresponding figures for the group vaccinated with vole bacillus were 77, 88, 68, 58, and (between 10 and 15 years) 73%. Thus the protective efficacy of each vaccine rose to a peak between 2½ and 5 years after vaccination, and decreased to lower levels subsequently. The decline in protection over the whole period (assessed by a χ^2 test for trend) was significant at the 2% level for both vaccines combined. However, the average protection from both vaccines was still substantial (63%) between 10 and 15 years after vaccination.

In this connexion it will be noted from the numbers of cases between 12½ and 15 years (Table 3) that, during this period, the incidence in the two vaccinated groups combined (6 cases in 19 415 participants) was similar to that in the tuberculin-negative unvaccinated group (5 cases in 12 867 participants). This could be interpreted as indicating a very low level of protection from the vaccines after 12½ years. Such an interpretation would be unwise, partly because the numbers are small and partly because the numbers of cases between 10 and 12½ years, if they are considered in isolation, imply a *higher* protection from the vaccines during this period than in the previous 5 years. It therefore seems likely that the average for 10 to 15 years is more trustworthy than the separate figures for the periods 10–12½ and 12½–15 years.

A few cases of tuberculosis have developed among participants between 15 and 20 years after entry to the trial, and have been reported to the MRC through the continuing arrangements with chest clinics and medical officers of health. The provisional totals of cases (not included in Table 3) are 6 in the two vaccinated groups combined and 4 in the tuberculin-negative unvaccinated group, suggesting no protection at all from vaccination beyond 15 years. However, these numbers are small, and no definite conclusion on the level of protection after 15 years can yet be drawn from them. Following the increase during the first 5 years (Table 4), the protection from vaccination in this trial has decreased only gradually, and may therefore not have disappeared completely by 15 years.

Among the groups with positive reactions to tuberculin initially, those with the largest reactions (induration of 15 mm or more with 3 TU) had an annual tuberculosis incidence of 3.75 per 1 000 during the first 2½ years—a rate substantially greater than that in the tuberculin-negative unvaccinated group (2.12 per 1 000) and very much greater than the rates in the other two initially tuberculin-positive groups (both 0.77 per 1 000). In this group with the largest initial reactions the incidence fell steeply in succes-

Table 4. Protective efficacy, over 15 years, of the BCG and vole bacillus vaccines given in the MRC trial[a]

Vaccine	Protective efficacy (%) at intervals (in years) after vaccination				
	0–	2½–	5–	7½–	10–15
BCG	81	87	70	68	59
Vole bacillus	77	88	68	58	73
Both	80	87	71	65	63

[a] See footnote *a*, Table 3.

sive periods to 1.83, 1.01, and 0.42; between 10 and 15 years it rose slightly, to 0.48 per 1 000. In the other two initially tuberculin-positive groups the rates first rose, then fell gradually. However, they have remained lower throughout than in the group with the largest initial reactions; between 10 and 15 years the annual incidence was 0.37 per 1 000 in those showing indurations of 5–14 mm with 3 TU and 0.23 per 1 000 in those who had positive reactions only to 100 TU.

It will also be noted that the rates in the vaccinated participants were, with one exception, lower than in any of the initially tuberculin-positive groups during the same period.

The timing of the cases of tuberculosis during the 15-year period of the trial varies with the form of the disease. Of the 406 cases of non-miliary pulmonary tuberculosis, 248 (61%) started during the first 5 years and only 36 (9%) between 10 and 15 years (these figures are not tabulated here). For the 85 cases of pleural effusion, the corresponding figures were 72% and 6%. Considering the two forms of tuberculosis that occurred with particular frequency among those who initially had positive reactions to 3 TU, tuberculous adenitis also showed a decreasing incidence during the 15 years (13, 5, and 4 cases in successive 5-year periods in this trial group), whereas genitourinary tuberculosis—unlike any other specific form—showed an increasing incidence (3, 4, and 9 cases in successive 5-year periods in this trial group, and 0, 1, and 5 cases in the other groups combined). The numbers of cases of bone-and-joint tuberculosis that occurred in successive 5-year periods in all the trial groups combined were 8, 5, and 1.

DEATHS IN THE TRIAL POPULATION

A total of 381 deaths within 15 years of entry have been reported among the trial participants. Because the follow-up was designed to ensure as complete a detection of *tuberculosis cases* as possible, and was not specifically directed towards deaths, this total may be incomplete. Mortality comparisons between the different trial groups are nevertheless valid because the follow-up was undertaken impartially in all groups.

Of the 381 deaths, 2 were due to tuberculosis (Great Britain, Medical Research Council, 1963). The remaining 379 correspond to an annual mortality of 46.5 per 100 000 in the whole trial population (Table 5). The corresponding figure for England and Wales (for the population cohort aged 15 on

Table 5. Deaths from causes other than tuberculosis within 15 years [a]

Trial group	Number of participants	Deaths within 15 years, according to cause [b]											
		All causes other than tuberculosis [a]		Neoplasms of lymphatic and haematopoietic tissues (200–205)		Other malignant neoplasms (140–199)		Respiratory diseases (470–527)		Other diseases		Violent causes (800–999)	
		No.	Rate[c]	No.	Rate[c]	No.	Rate[c]	No.	Rate[c]	No.	Rate[c]	No.	Rate[c]
Negative, unvaccinated	12 867	92	47.7	8	4.1	4	2.1	5	2.6	31	16.1	44	22.8
Negative, BCG-vaccinated	13 598	93	45.6	6	2.9	7	3.4	3	1.5	24	11.8	53	26.0
Negative, vaccinated with vole bacillus	5 817	34	39.0	1	1.1	3	3.4	3	3.4	12	13.8	15	17.2
Positive to 3 TU	15 704	113	48.0	9	3.8	17	7.2	4	1.7	33	14.0	50	21.2
Positive only to 100 TU	6 253	47	50.1	5	5.3	5	5.3	3	3.2	14	14.9	20	21.3
All groups	54 239	379	46.5	29	3.6	36	4.4	18	2.2	114	14.0	182	22.4
England and Wales—cohort aged 15 years on 1 January 1952	—	—	73.0	—	4.3	—	5.9	—	4.6	—	26.1	—	32.1

[a] There were 2 deaths from tuberculosis within 15 years (Great Britain, Medical Research Council, 1963).
[b] WHO (1957) Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, 7th ed., Geneva.
[c] Annual mortality per 100 000 population.

1 January 1952, followed up for 15 years) was 73.0. Nearly half the deaths (182, or 22.4 per 100 000) were due to violent causes, and this rate is less by 30% than that for the whole country (32.1). However, the deficit in the rate for medical causes of death is larger (41%), and this suggests that the trial population may have been rather healthier than the general population.

Of the 197 deaths from diseases other than tuberculosis, 18 were due to other respiratory diseases, 29 to neoplasms of lymphatic and haematopoietic tissues, and 36 to other malignant neoplasms. The mortality from neoplasms of the lymphatic and haematopoietic tissues was lower in the two vaccinated groups than in the tuberculin-negative unvaccinated group (2.4 per 100 000 for the vaccinated groups combined, compared with 4.1). In contrast, the mortality from other malignant neoplasms was higher in the vaccinated than in the tuberculin-negative unvaccinated group (3.4 compared with 2.1). Neither difference is statistically significant. However, it will be noted that the mortality from all malignant neoplasms was greater among those who were initially tuberculin-positive (36 among 21 957 subjects) than among those who were initially tuberculin-negative (29 among 32 282 subjects); the chance probability of obtaining so large a difference is about 1 in 50 (corrected $\chi^2 = 5.40$ with 1 degree of freedom).

REVIEW OF THE TRIAL

In 1949–50, when this trial was being planned, tuberculosis was still a major clinical and public health problem in Great Britain, although the situation was more favourable than in many other countries. Thus there were 19 721 deaths from the disease in England and Wales in 1949 (compared with only 1 840 in 1969); effective chemotherapy, with streptomycin and para-aminosalicylic acid, had only recently been introduced, and preventive measures such as the eradication of bovine tuberculosis in cattle were far from complete. Although BCG vaccination had been accepted in many countries as an effective method of protecting the individual against progressive tuberculosis, it had been adopted to only a limited extent in Great Britain. There was still disagreement on the value of the vaccine, and there was therefore a pressing need for an adequate study of the contribution that vaccination could make to the control of tuberculosis in this country.

To this end the Committee decided to study the effects of vole bacillus vaccine as well as the BCG vaccine, under ordinary conditions of life not in groups at special risk of exposure to the d... It was particularly important to assess the degree duration of protection from each vaccine in a... cence, since the notification rate and mortality tuberculosis began to rise from their low chil... levels at about the age of 15 years. For this r... the trial was begun in children during their ... year at school, and an intensive follow-up ... participants was arranged, which has now ... maintained effectively for more than 15 ... Information has therefore accrued, in an indu... community with well-developed health service... the degree and duration of protection from a ... vaccination at about the age of 15, up to the ... 30 years, in the face of a moderately low and, ... since been realized, steadily decreasing gener... of tuberculous infection.

The features of this trial that have ensured ... validity of the conclusions to be drawn from it ... (1) the random allocation of the initially tuberc... negative participants to the two vaccinated grou... and to the unvaccinated control group; (2) ... intensive follow-up that has been applied impartia... to all the participants in the trial including ... found to be tuberculin-positive initially; (3) ... method of unbiased assessment of the case... tuberculosis that developed, by an assessor ... was kept unaware of the results of any tuberc... tests and whether any vaccination had been ... formed; and (4) the large number of participa... The random allocation scheme worked well ... practice. The small numbers of subjects who ... incorrectly vaccinated or left unvaccinated, or ... refused vaccination, although they were follow... during the trial, have been excluded from the a... of the findings (Great Britain, Medical Re... Council, 1963). The follow-up and the case-fi... procedures were shown to have been equally int... in practice in all the trial groups from the out... the trial (Great Britain, Medical Research Co... 1956, 1959). A special examination of other ... sible sources of bias in the reporting of cases ... independent assessor—namely, knowledge ... participant of his skin-test and vaccination ... or similar knowledge on the part of the Na... Health Service physician or the MRC physici... diagnosed the case—has also given positive evi... that no serious bias entered into the compa... between the unvaccinated and vaccinated g...

Great Britain, Medical Research Council, 1959).

It is therefore justifiable to conclude that the differences in the incidence of tuberculosis between the tuberculin-negative unvaccinated and the vaccinated groups may be attributed with confidence to vaccination. Similarly, the differences between the incidence in the tuberculin-negative unvaccinated and the two tuberculin-positive groups may be attributed to differences in tuberculin sensitivity as well as to the (unknown) previous circumstances that produced the sensitivity.

FINDINGS OF THE TRIAL

The 15-year findings of the trial in relation to tuberculosis may be summarized as follows:

1. BCG vaccination conferred substantial protection against tuberculosis. The reduction in the incidence of tuberculosis attributable to BCG vaccination (the protective efficacy) was 78.4% for the 15-year period following vaccination. Making allowance for chance fluctuations in the numbers of cases observed (using Fieller's theorem) it may be claimed with a high degree of confidence (99%) that the protective efficacy of BCG vaccine lay between 69% and [illegible].

2. The substantial protection from BCG vaccine extended to all forms of tuberculosis. For tuberculous meningitis and miliary pulmonary tuberculosis it was complete; there were 10 cases in unvaccinated, and none in vaccinated, participants.

3. The protection from BCG vaccine was similar in both sexes.

4. The protective efficacy of BCG vaccine exceeded 80% during the first 5 years after vaccination, and then decreased gradually. The efficacy was still high (59%) between 10 and 15 years after vaccination; no definite conclusion can yet be reached on the level of protection after 15 years. The factors underlying this decrease are discussed below.

5. Vole bacillus vaccine conferred as substantial a protection against tuberculosis as did BCG vaccine. The protective efficacy of vole bacillus vaccine was 80.8% for the 15-year period following vaccination, with 99% confidence limits of 68% and 91%. In terms of protection against different forms of tuberculosis, protection in the two sexes, and the trend in protective efficacy during the 15 years, vole bacillus vaccine was closely similar to BCG vaccine.

A disadvantage of some of the batches of vole bacillus vaccine was the very occasional development at the vaccination site of lesions resembling lupus vulgaris. This occurred only with the later batches of the vaccine, prepared from substrains 2–4, which gave high levels of postvaccination tuberculin sensitivity and also a high degree of protection against tuberculosis. Substrain 1, in both low and high doses, had given low levels of postvaccination sensitivity, and was replaced by the other substrains for that reason, but was subsequently also found to have conferred a high degree of protection against tuberculosis without the infrequent complication of lupus with either dose (Mitchell, 1962; Hart et al., 1967). In a full review of the findings with vole bacillus vaccine, both in this trial and by other workers, Mitchell (1962) concluded that "the development of lupus at the vaccination site may now be considered to be of historical interest only and is no longer a contraindication to the use of vole bacillus vaccine as a vaccinating agent in the future" (see also Hart & Sutherland, 1969). Vole bacillus vaccine has a potential advantage over BCG vaccine because its virulence can be restored if necessary by passage through its natural host (Wells, 1946). Since at least one substrain of vole bacillus vaccine (which is still available[1]) has been shown to confer substantial protection against tuberculosis without the complication of lupus, it would seem to be worth considering the reintroduction of the vole bacillus as an immunizing agent against tuberculosis.

6. There was a particularly high incidence of tuberculosis during the first 2½ years among those with the largest reactions to tuberculin initially, reflecting active infections acquired before the start of the trial (Great Britain, Medical Research Council, 1959). Among those with smaller reactions to tuberculin initially, the incidence of tuberculosis was considerably lower throughout the trial than in the tuberculin-negative unvaccinated group. Low-grade tuberculin sensitivity, which in Great Britain is partly tuberculous in origin and partly due to other mycobacteria (Hart et al., 1962; Sutherland et al., 1964), is thus associated with a naturally acquired specific immunity against fresh exogenous tuberculous infections (Great Britain, Medical Research Council, 1959). However, the natural immunity acquired by the groups with low-grade sensitivity could not have been as great as the immunity conferred by vaccination on the vaccinated groups,

[1] This strain of *Mycobacterium microti* is maintained in freeze-dried form (reference no. NCTC 8712) in the National Collection of Type Cultures at the Central Public Health Laboratory, Colindale Avenue, London, England.

since the latter experienced the lowest incidences of tuberculosis throughout the trial.

7. In successive 5-year periods, there was a steep decrease in the incidence of every form of tuberculosis except for the genitourinary form, of which 3, 5, and 14 cases developed in successive 5-year periods. Moreover, 16 of these 22 cases occurred among participants who had shown a positive reaction to a low dose of tuberculin on entry to the trial. These findings demonstrate that genitourinary tuberculosis frequently takes many years to develop following primary infection.

VACCINATION AND DISEASES OTHER THAN TUBERCULOSIS

The trial has also provided information on the value of BCG and vole bacillus vaccination in relation to diseases other than tuberculosis. Neither vaccine appeared to be effective against other respiratory diseases, either in terms of the cases submitted to the trial assessor (Great Britain, Medical Research Council, 1959, 1963) or in terms of deaths (this report); nor was any benefit from vaccination apparent with sarcoidosis cases (Sutherland et al., 1965) or with deaths from any other specific cause (this report), with the possible exception of leukaemia.

The suggestion that BCG vaccination might protect against leukaemia, or might influence the course of the disease, was originally advanced by Mathé et al. (1967). More recently Davignon et al. (1970, 1971) have found that in the province of Quebec the incidence of leukaemia in the first 5 years of life is about half as great in children given BCG vaccine at birth as in those left unvaccinated. In the present trial, the mortality from neoplasms of lymphatic and haematopoietic tissues between the ages of 15 and 30 years was 2.4 per 100 000 per year (7 deaths) in the two vaccinated groups combined and 4.1 per 100 000 per year (8 deaths) in the tuberculin-negative unvaccinated group. The difference is of the same order of magnitude as that found by Davignon et al. (1970, 1971) but is not statistically significant. Hence the figures from the present trial, although small, support the findings in Quebec. However, Comstock et al. (1971), in a similar analysis of twice as many cases of leukaemia, Hodgkin's disease, and lymphosarcoma in a controlled trial of BCG vaccination in Georgia and Alabama (Comstock & Palmer, 1966) found "no indication that BCG vaccination had either prevented or encouraged the development of these diseases".

The finding of a higher mortality from all neoplasms among those initially tuberculin-positive than among those initially tuberculin-negative may reflect environmental or other differences between these two groups before entry to the present trial rather than a specific deleterious effect of mycobacterial infection; or it may simply represent an exceptional chance fluctuation.

OTHER CONTROLLED TRIALS OF BCG VACCINATION

In the first and second reports of this trial (Great Britain, Medical Research Council, 1956, 1959) reference was made to some of the other controlled trials of BCG vaccination. Information on six such trials is summarized in Table 6 together with the results of the present trial, and includes the most recently published findings, notably those of the first US Public Health Service trial of the vaccine not referred to in previous reports of this Committee (Shaw, 1951; Comstock & Shaw, 1960; Comstock & Webster, 1969). The variation in protective efficacy found for BCG vaccine in these trials is enormous, ranging from 80% in the trial in North American Indians to no protection at all in the first US Public Health Service trial in Georgia. All the trials incorporated safeguards against bias in the results, and there is no evidence of methodological shortcomings in any of them that could account for the differences in efficacy.

The possibility that nutritional differences between the various population groups might have contributed to the differences in efficacy (Dubos, 1964) has been considered and dismissed as a major determinant of those differences (Hart & Sutherland, 1965; Hart, 1967).

It has been suggested (Palmer & Long, 1966; Ferebee & Palmer, 1966) that the differences in efficacy in the British trial and in the US Public Health Service trials could be explained by differences in the frequency of nonspecific mycobacterial infections in the two areas, together with differences in the criteria of eligibility for vaccination in the trials. As a result of these differences, it was assumed a large proportion of the vaccinated groups in the American areas had already acquired some immunity from nonspecific mycobacterial infections. Thus, by analogy with findings in guinea-pigs (Palmer & Long, 1966), BCG vaccine could add relatively little immunity to this. In contrast, a much lower proportion of

Table 6. Summary and results of 7 controlled trials of BCG vaccination against tuberculosis

Population group and reference	Period of intake and age range	Criterion of eligibility for vaccination	Source of vaccine	Duration of follow-up (years)	Vaccination group	No. of subjects	Cases of tuberculosis		Protective efficacy (%)
							No.	Rate [a]	
North American Indians (8 tribes) (Stein & Aronson, 1953)	1935–38 0–20 years	negative to 0.005 mg PPD-Seibert (250 TU)	Henry Phipps Institute, Philadelphia	9–11	unvaccinated	1 457	238	1 563	80 [b]
					BCG	1 551	64	320	
Chicago infants, high-risk areas (Rosenthal et al., 1961)	1937–48 under 3 months	no initial tuberculin testing	Tice Laboratory, Chicago [c]	12–23	unvaccinated	1 665	66	223 [d]	75
					BCG	1 716	17	67 [d]	
Georgia, general population (Comstock & Webster, 1969)	1947 6–17 years	under 5 mm to 0.002 mg RT 18 (100 TU)	Tice Laboratory, Chicago [c]	20	unvaccinated	2 361	3	11	none
					BCG	2 498	5	17	
Puerto Rico, general population (Palmer et al., 1958)	1949–51 1–18 years	Under 6 mm to 0.0002 mg RT 19–20–21 (10 TU)	State Department of Health, New York	5 ½–7 ½ (mean : 6.3)	unvaccinated	27 338	73	43	31
					BCG	50 634	93	30	
Georgia, Alabama, general population (Comstock & Palmer, 1966)	1950 5 years and over	Under 5 mm to 0.0001 mg RT 19–20–21 (5 TU)	Tice Laboratory, Chicago [c]	14	unvaccinated	17 854	32	13	14
					BCG	16 913	26	11	
Great Britain, urban populations (this report)	1950–52 14–15 ½ years	Under 5 mm to 0.1 ml 1/100 Old Tuberculin (100 TU)	Statens Serum-institut, Copenhagen	15	unvaccinated	12 699	240	128	78
					BCG	13 598	56	28	
South India, rural population (Frimodt-Møller et al., 1968)	1950–55 all ages	Under 5 mm to 5 TU RT 19–20–21	BCG Laboratory, Madras	9–14 (mean : 12.3)	unvaccinated	5 808	46	89	31
					BCG	5 069	28	61	

[a] Annual rate per 100 000 population, usually allowing for losses from observation.

[b] The protective efficacy against death from tuberculosis was 82 % for a period of 18–20 years (Aronson et al. 1958).

[c] This laboratory has issued a number of strains at different times and it is not known whether the strains used in these three trials were the same or not.

[d] Assuming a mean observation period of 17.5 years.

those vaccinated in the British trial already had some naturally acquired immunity from other mycobacterial infections, and were therefore able to show a greater response to BCG vaccination. It has since been confirmed (Edwards & Palmer, 1968) from the results of dual tuberculin tests that human beings with evidence of past infection with atypical mycobacteria of the Battey type are less likely to develop tuberculosis subsequently than those without evidence of any past mycobacterial infection—presumably as a result of a naturally acquired immunity from the Battey infection.

However, in a detailed analysis of this proposition, Hart (1967) showed that it was inadequate to provide a complete explanation of the difference between the American and British findings, and suggested that in addition the vaccines used in the American trials may not have been as potent as the Danish substrain of BCG used in the British trial. Variations in potency between strains from the different laboratories supplying the American trials, bearing some relation to the variations in efficacy shown in Table 5 (Hart, 1967), were found in guinea-pigs by Willis et al. (1960) and Willis and Vandiviere (1961); however, these tests were made some years after the trials and cannot be regarded as conclusive.

An analysis of the tuberculosis notifications and vaccination records in Birmingham between 1953 and 1969 (Springett & Sutherland, 1970) should also be noted. This was not a controlled trial, but a comparison of the tuberculosis incidence in subjects given BCG vaccine in the national scheme and in those who did not participate in this scheme. It confirmed that the batches of liquid BCG vaccine [1] used in Birmingham from 1953 to 1961 were no less effective in preventing tuberculosis than the earlier batches of this product used in the MRC trial during the period 1950–52. Moreover, the batches of freeze-dried BCG vaccine [2] used in Birmingham from 1962 to 1968 also had a high degree of efficacy against tuberculosis, similar to that of the earlier batches of liquid vaccine from the Copenhagen strain. Springett and Sutherland (1970) therefore provide supporting evidence of the continuing effectiveness of BCG vaccine in the prevention of tuberculosis in Great Britain, notwithstanding the variations in efficacy found in other parts of the world. In addition, the study has demonstrated for the first time the high protective efficacy of Glaxo BCG against tuberculosis in Great Britain; this vaccine is used routinely in this country and also in others throughout the world.

[1] Statens Seruminstitut, Amager Boulevard 80, Copenhagen, Denmark.

[2] Glaxo Laboratories, Ltd., Greenford, Middlesex, England.

THE TRENDS IN TUBERCULOSIS INCIDENCE IN THE VACCINATED AND UNVACCINATED GROUPS

The influences that could have contributed to the observed trends in the incidence of tuberculosis in the vaccinated and unvaccinated groups were set out in detail in a previous report (Great Britain, Medical Research Council, 1963). They include four influences that might be expected to have affected the vaccinated and unvaccinated groups equally: (1) a general reduction with time in the risk of tuberculous infection; (2) changes in exposure to infection with increasing age; (3) changes in physiological susceptibility to disease following infection, with increasing age; and (4) changes in the efficiency of the case-finding procedures during the trial. In addition, there are four influences that might have affected the vaccinated and unvaccinated groups differentially: (5) changes in the efficacy of the vaccine in the vaccinated subjects; (6) a differential increase in the level of resistance of each group by removal of the more susceptible subjects who contract tuberculosis; (7) a differential increase in resistance due to the immunity conferred by natural infections (whether these were tuberculous and did not lead to clinical tuberculosis, or were due to other mycobacteria); and (8) a difference in the mean period of latency between infection and clinical disease.

As regards the first four influences, it seems probable that a general reduction in the risk of tuberculous infection during the 15-year period has been the main factor underlying the decreasing incidence of tuberculosis in the unvaccinated subjects.

The second four influences together could have accounted for the contrasting trends in incidence between the vaccinated groups and the tuberculin-negative unvaccinated group, but their relative effects are uncertain. Thus, there has probably been a general increase in the immunity of the unvaccinated group as the trial proceeded, owing to primary tuberculous infections that did not result in clinical tuberculosis and to other mycobacterial infections (e.g., infections with atypical mycobacteria). This increase in immunity, if it is not shared by the vaccinated groups (although they have been similarly exposed to tuberculous and other mycobacterial infec-

tions), would give the impression of a decrease in the efficacy of the vaccines, even if there had been no change in the protection conferred on the vaccinated subjects. Alternatively, or as well, there may have been a waning in the efficacy of the vaccine or a longer period of latency in the vaccinated than in the unvaccinated cases. But, whatever the full explanation may be for the gradual convergence of the rates in the vaccinated and unvaccinated groups, the present trial has demonstrated clearly that, in Great Britain, the use of BCG vaccine and vole bacillus vaccine, given as artificial immunizing agents during the period 1950–52 to adolescents aged about 15 years, has led to a substantial reduction in tuberculosis for a period of 15 years.

THE APPLICABILITY OF TUBERCULOSIS VACCINATION

In previous reports (Great Britain, Medical Research Council, 1956, 1959) the benefit from vaccination in the trial population was expressed in terms of the reduction in incidence to be expected in the whole trial population, including persons who were tuberculin-positive on entry and therefore ineligible for vaccination. Since the incidence among those initially tuberculin-positive would not be directly affected by vaccination, the percentage benefit in the whole population must be less than the percentage efficacy found for the vaccinated group alone.

Because of the radical changes that have taken place in the tuberculosis situation in Great Britain since 1950, a similar assessment of the reduction in tuberculosis in the whole trial population over this 15-year period would have no special relevance to an assessment of the present value of tuberculosis vaccination in this country. It is preferable to consider the expected benefit, or the " applicability ", of mass vaccination in more general terms. Hart (1967) has shown that the applicability of vaccination, calculated as the absolute reduction in the annual incidence of tuberculosis in the whole population as a result of vaccinating all those regarded as eligible for vaccination, is the product of three factors: (1) the protective efficacy of the vaccine among those eligible; (2) the expected annual incidence of tuberculosis in those eligible, if they are left unvaccinated; and (3) the proportion of the population who are regarded as eligible. Of these three factors, the incidence in those eligible but left unvaccinated is likely to vary more widely than the other two factors if a potent vaccine is used, and so will be the main determinant of the benefit to be expected from vaccination. Therefore, from estimates of the three factors in any given epidemiological situation, it is possible to assess the reduction in tuberculosis to be expected from a mass vaccination scheme.

* * *

Members of the Committee: Dr P. D'Arcy Hart (Chairman), Dr J. R. H. Berrie, Dr C. Metcalfe Brown, Professor R. Cruickshank, Dr Wallace Fox, Dr J. E. Geddes, Sir Austin Bradford Hill, Dr T. M. Pollock, Dr V. H. Springett, Sir Graham Wilson, and Dr Ian Sutherland (Secretary). The following have also served on the Committee at various times: Sir John Charles, Dr Marc Daniels, Dr W. Pointon Dick, Dr A. J. Eley, Sir Wilson Jameson, Dr D. Thomson, and Dr A. Q. Wells.

The trial was originally co-ordinated by the late Dr Marc Daniels and then by Dr T. M. Pollock; from 1960 to 1968, it was supervised by Dr D. N. Mitchell and Dr Christine L. Miller. Since 1968, Dr Miller (now at the Central Public Health Laboratory, London) has supervised the trial on behalf of the Tuberculosis and Chest Diseases Unit, Medical Research Council (MRC). Dr V. H. Springett has served throughout as the principal independent assessor.

The report was prepared for the Committee by Dr Ian Sutherland (MRC Statistical Research and Services Unit).

ACKNOWLEDGEMENTS

Detailed acknowledgements to those who assisted in the early stages of the trial and in the follow-up until September 1960 appear at the end of the first and second reports (Great Britain, Medical Research Council, 1956, 1959).

Since then, special quarterly returns of cases of tuberculosis have been made to the MRC by every chest clinic and medical officer of health in Great Britain. Similar returns were made from many large hospitals in the original trial areas for 1966 and 1967. The Committee wishes to thank all those who have been concerned with this essential reporting.

Throughout this period the secretarial and clerical work of the trial has been ably co-ordinated by Mrs A. Allchin (Central Public Health Laboratory, London; formerly MRC Tuberculosis and Chest Diseases Unit). The Com-

mittee thanks the Public Health Laboratory Service and Dr T. M. Pollock (Director, Epidemiological Research Laboratory, Central Public Health Laboratory) for housing the central record office for the trial from October 1968.

Finally, the Committee thanks all the participants for their lasting interest and co-operation in the trial, as a result of which it was possible to continue the individual follow-up for five times as long as was originally envisaged.

RÉSUMÉ

RÔLE DU BCG ET D'UN VACCIN PRÉPARÉ À PARTIR D'UNE SOUCHE MURINE DE BACILLE TUBERCULEUX DANS LA PRÉVENTION DE LA TUBERCULOSE CHEZ L'ADOLESCENT ET LE JEUNE ADULTE

Le Comité des essais cliniques de vaccins antituberculeux publie ici son 4e rapport au Medical Research Council de Grande-Bretagne. Les investigations dont il est fait mention, destinées à étudier les effets préventifs de la vaccination par le BCG ou par un vaccin antituberculeux d'origine murine, portent sur un total de 54 239 enfants des deux sexes qui ont été suivis pendant 15 ans.

Durant cette période, on a enregistré dans l'ensemble des participants 583 atteintes de tuberculose; dans 70% des cas, il s'agissait de tuberculose pulmonaire et dans 15% des cas d'épanchement pleural tuberculeux sans signes de lésions pulmonaires. Parmi les 13 598 sujets vaccinés par le BCG, l'incidence annuelle de la tuberculose a été de 0,28 pour 1000; elle a atteint 1,28 pour 1000 chez les sujets tuberculinonégatifs non vaccinés et inclus dans l'étude en même temps; la réduction de l'incidence dans le 1er groupe est de 78,4%. Parmi les 5817 sujets vaccinés par le vaccin murin, l'incidence a été de 0,29 pour 1000, alors qu'elle s'est élevée à 1,50 pour 1000 chez les sujets tuberculinonégatifs non vaccinés, soit une réduction de 80,8%. Etant donné les conditions de l'enquête (répartition aléatoire des sujets tuberculinonégatifs dans les groupes vaccinés et non vaccinés, observation objective de tous les participants, diagnostic sans parti pris des cas de tuberculose), ces réductions reflètent sans aucun doute le pouvoir protecteur élevé des deux vaccins.

La protection s'est manifestée à l'égard de toutes les formes de tuberculose. C'est ainsi qu'on a enregistré 10 cas de méningite tuberculeuse ou de tuberculose pulmonaire miliaire chez les sujets non vaccinés et aucun chez les sujets vaccinés. Bien que l'effet préventif de la vaccination ait décru progressivement durant la période d'observation, il était encore très net entre la 10e et la 15e année (taux de protection conféré par le BCG: 59% et par le vaccin murin: 73%). Il est trop tôt pour évaluer avec exactitude le degré de protection après 15 ans.

Chez les sujets fortement positifs lors de l'admission dans l'étude (réaction de 15 mm ou plus après injection de 3 UT de vieille tuberculine), l'incidence annuelle de la tuberculose a été particulièrement élevée (3,75 pour 1000) au cours des deux premières années et demie, objectivant ainsi des infections évolutives acquises antérieurement. Chez ceux qui réagissaient plus faiblement à la tuberculine lors de l'admission, l'incidence s'est constamment maintenue à un niveau plus faible que dans le groupe des sujets tuberculinonégatifs non vaccinés. A un faible niveau de sensibilité tuberculinique correspondait donc un certain degré d'immunité naturellement acquise, de valeur moindre cependant que celui conféré par la vaccination.

Au cours des 15 années, on a noté un déclin abrupt de l'incidence des diverses formes de la tuberculose sauf en ce qui regarde la tuberculose génito-urinaire; au cours des trois périodes successives de 5 ans, 3,5 et 14 cas de cette forme de l'affection ont été enregistrés, principalement parmi les sujets initialement tuberculinopositifs.

Aucun des deux vaccins n'a fait preuve d'une action préventive à l'égard des affections non tuberculeuses de l'appareil respiratoire, de la sarcoïdose ou d'autres maladies. Il semble cependant, d'après un petit nombre de données, qu'une vaccination unique par le BCG, à l'âge de 15 ans, pourrait protéger contre la leucémie. La mortalité par tumeurs de tous types a été significativement plus élevée parmi les sujets initialement tuberculinopositifs que parmi les sujets tuberculinonégatifs (antérieurement vaccinés ou non).

Le rapport fournit un résumé des résultats d'ensemble de l'étude. On y trouve aussi des considérations sur la place de la vaccination par les souches murines du bacille tuberculeux, une étude comparative des données relatives au BCG recueillies au cours du présent essai et de six autres essais contrôlés, des hypothèses concernant l'évolution de la maladie tuberculeuse dans les groupes vaccinés et non vaccinés, et l'exposé d'une méthode pour évaluer l'opportunité de la vaccination de masse par le BCG dans une situation épidémiologique donnée.

REFERENCES

Aronson, J. D., Aronson, C. F., & Taylor, H. C. (1958) *Arch. intern. Med.*, **101**, 881

Comstock, G. W., Livesay, V. T., & Webster, R. G. (1971) *Lancet*, **2**, 1062

Comstock, G. W. & Palmer, C. E. (1966) *Amer. Rev. resp. Dis.*, **93**, 171

Comstock, G. W. & Shaw, L. W. (1960) *Publ. Hlth Rep. (Wash.)*, **75**, 583

Comstock, G. W. & Webster, R. G. (1969) *Amer. Rev. resp. Dis.*, **100**, 839

Davignon, L., Lemonde, P., Robillard, P. & Frappier, A. (1970) *Lancet*, **2**, 638

Davignon, L., Lemonde, P., St-Pierre, J. & Frappier, A. (1971) *Lancet*, **1**, 80

Dubos, R. (1964) *Amer. Rev. resp. Dis.*, **90**, 505

Edwards, L. B. & Palmer, C. E. (1968) *Ann. N.Y. Acad. Sci.*, **154**, 140

Ferebee, S. H. & Palmer, C. E. (1966) In: Gaubatz, E. et al., ed., *Die Tuberkulose und ihre Grenzgebiete in Einzeldarstellungen*, Berlin, Vol. 18, p. 105

Frimodt-Møller, J., Acharyulu, G. S., & Parthasarathy, R. (1968) *Ind. J. Tuberc.*, **15**, 40

Great Britain, Medical Research Council (1956) *Brit. med. J.*, **1**, 413

Great Britain, Medical Research Council (1959) *Brit. med. J.*, **2**, 379

Great Britain, Medical Research Council (1963) *Brit. med. J.*, **1**, 973

Hart, P. D'Arcy (1967) *Brit. med. J.*, **1**, 587

Hart, P. D'Arcy, Miller, C. L., Sutherland, I., & Lesslie, I. W. (1962) *Tubercle (Edinb.)*, **43**, 268

Hart, P. D'Arcy & Sutherland, I. (1965) *Amer. Rev. resp. Dis.*, **91**, 939

Hart, P. D'Arcy & Sutherland, I. (1969) *Brit. med. J.*, **2**, 54

Hart, P. D'Arcy, Sutherland, I. & Thomas, J. (1967) *Tubercle (Edinb.)*, **48**, 201

Mathé, G., Schwarzenberg, L., Amiel, J. L., Schneider, M., Cattan, A., Schlumberger, J. R., Tubiana, M. & Lalanne, C. (1967) *Scand. J. Haemat.*, **4**, 193

Mitchell, D. N. (1962) *A re-assessment of the potentialities of vole bacillus vaccine in the protection against tuberculosis*, London (Thesis)

Palmer, C. E. & Long, M. W. (1966) *Amer. Rev. resp. Dis.*, **94**, 553

Palmer, C. E., Shaw, L. W. & Comstock, G. W. (1958) *Amer. Rev. Tuberc.*, **77**, 877

Rosenthal, S. R., Loewinsohn, E., Graham, M. L., Liveright, D., Thorne, M. G., Johnson, V. & Batson, H. C. (1961) *Pediatrics*, **28**, 622

Shaw, L. W. (1951) *Publ. Hlth Rep. (Wash.)*, **66**, 44

Springett, V. H., & Sutherland, I. (1970) *Brit. med. J.*, **4**, 148

Stein, S. C. & Aronson, J. D. (1953) *Amer. Rev. Tuberc.*, **68**, 695

Sutherland, I., Miller, C. L., Hart, P. D'Arcy & Lesslie, I. W. (1964) *Tubercle (Edinb.)*, **45**, 110

Sutherland, I., Mitchell, D. N. & Hart, P. D'Arcy (1965) *Brit. med. J.*, **2**, 497

Wells, A. Q. (1946) *The murine type of tubercle bacillus*, London (*Spec. Rep. Ser. med. Res. Counc. (Lond.)*, 259)

WHO (1957) *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*, 7th ed., Geneva

WHO Expert Committee on Tuberculosis (1964) *Wld Hlth Org. techn. Rep. Ser.*, No. 290

Willis, H. S., Vandiviere, H. M., Vandiviere, M. R. & Melvin, I. (1960) *Amer. J. med. Sci.*, **240**, 137

Willis, S. & Vandiviere, M. (1961) *Amer. Rev. resp. Dis.*, **84**, 288

Indian J Med Res 70, September 1979, pp 349-363

Trial of BCG vaccines in south India for tuberculosis prevention

Tuberculosis Prevention Trial, Madras.*

Received August 1, 1979.

The protective effect of BCG vaccination is being evaluated in a controlled community trial near Madras in south India. After tuberculin and sensitin testing and radiographic and bacteriological examination, BCG vaccines and placebo were allocated randomly to about 260 000 individuals, of whom 115 000 were definitely tuberculin negative at the time of vaccination. Intensive efforts are being made, by means of regular follow-up surveys, to identify all new cases of tuberculosis occurring in the community. This report presents findings of the first 7½ years of follow-up. Incidence of infection was high in the study population. However, incidence of bacillary disease was more frequent among initial tuberculin reactors, especially among the older persons, than among non-reactors of whom the majority were in the younger age groups. The distribution of new cases of bacillary tuberculosis among those not infected at intake did not show any evidence of a protective effect of the BCG vaccines.

Although BCG vaccine has been in use for over 50 years, its mode of action—and indeed the immune mechanism in tuberculosis—has remained largely obscure. In particular, it has not been possible to quantify, or even identify, the critical factors that govern the level of protection BCG vaccination can confer to man. That such factors must exist has emerged from the results of controlled field trials, which showed protection ranging from none to as much as 80 per cent. Unfortunately, the results of the trials offer only a few pointers, since the trials were independent and factors that are possibly relevant were confounded in the individual designs[1].

*The Tuberculosis Prevention Trial, Madras, is a project carried out under the auspices of the Indian Council of Medical Research in collaboration with the World Health Organization, and (until June 1976) the Center for Disease Control, US Public Health Service, USA. This article is an abridged version of a comprehensive report, prepared by Dr. G.V.J. Bally, Project Director, Dr. Raj Narain, formerly Project Director, Dr. S. Mayurnath, Assistant Project Director, Shri R.S. Vallishayee, Senior Statistician and Dr. J. Guld, Consultant, World Health Organization. Bacteriological investigations were carried out during intake at the Union Mission Tuberculosis Sanatorium (Director at that time : Dr. J Frimodt Möller), Madanapalle, Tamil Nadu, and later at the Tuberculosis Research Centre (Director : Dr. S.P. Tripathy), Madras.

The following sources of variation may ve been important: the vaccines for the ferent trials were prepared in different oratories from cultures that had been pagated for many years and had there- e been subject to mutation and selection mutants (in fact, the original BCG strain not, strictly speaking a 'strain' accord- to present standards, since it was not ived from a single colony but from a ole culture[2]; differences in immuno- ticity and virulence among the strains d in some of the trials could be demons- ted in experimental animal models, l the potency differences observed in se models were closely associated with observed differences in protection[3–6]; l differences in the production methods ncentration, viability) and the dosages. trospective analysis of one trial, how- r, showed that the influence of these ter factors appeared to be fairly margi- l for the BCG vaccine concerned[7]. us, the strain could indeed be an im- rtant variable. This is also suggested the fact that, for the trials in which G vaccination appeared ineffective[8–10], vaccine had been prepared by the same oratory. On the other hand, vaccine m this laboratory proved highly effec- in another trial[11]. In a further l[12], two very different vaccinations h BCG and vole bacillus vaccines (the mer by injection, the latter by multiple ncture) appeared to give the same level protection. The actual relevance of vaccine strain to the protective effect in n therefore remains problematic.

A further factor invoked retrospectively the presence, in some of the study pulations, of sensitization by mycobac- ia other than the tubercle bacillus. It s been suggested that such sensitization could be associated with protection against tuberculosis and possibly could mask the protective effect of BCG vaccination. That hypothesis was confirmed in experiments in mice[13] and in guineapigs[14] in which a variety of saprophytic mycobacteria were shown to induce different levels of protection against virulent challenge, and in which additional vaccination with BCG appeared not to induce a higher level of protection than vaccination with BCG alone. This was borne out in a surveillance programme of naval personnel[15]. In the trials in which BCG vaccination proved ineffective, or had a low effectiveness, the presence of non-specific sensitivity was indeed demonstrated, but detailed quantitative analyses showed that non-specific sensitivity alone could not have masked completely the effect of a vaccine that would have had a high efficacy in a nonsensitized population[1,16]. Also, in one trial in which a modest protection was observed, this applied equally to the populations with and without low grade sensitivity[17].

Finally, it should be mentioned that one factor, the presence or absence of tuberculous infection in the trial subjects was, in fact, considered, in relation to selection of subjects, in all the trials. However, in view of the very rationale for vaccination against tuberculosis, this factor was implicitly assumed to play such an important role that no attempts were made to investigate it further; infected subjects have invariably been excluded from vaccination trials.

Neither the empirical findings of the field trials nor other epidemiological observations gave any indication of further relevant factors, but lack of detailed epidemiological knowledge could well have been important in this respect. The apparently conflicting trial results, as well as the fact that the vaccines employed in the trials cannot be reproduced, called for further and more systematic research. To some extent this had become easier because of the technical progress made meanwhile in the preparation of BCG vaccine. Freeze-drying techniques had been developed that made it possible to prepare a stable product from any BCG strain, and to maintain the strains as seed lots without the risk of further genotypic alterations[18]. Accordingly, there was a need to undertake further field trials with vaccines prepared from different seed lots and in different dosages, and to conduct these trials in populations in which nonspecific tuberculin sensitivity was present and in others, in whom it was absent. The incidence of tuberculosis in the study populations should be fairly high, and BCG vaccination should not be a current public health measure. A trial satisfying most of these conditions was organized in south India by the Indian Council of Medical Research (ICMR), in cooperation with the World Health Organisation (WHO) and the Center of Disease Control, US Public Health Service, in a population in which nonspecific tuberculin sensitivity was highly prevalent. Unfortunately, a contrasting area in which nonspecific tuberculin sensitivity was of low prevalence, or even absent, could not be identified in India, at that time.

Material and Methods

Trial location and population : The trial area included a total population of about 360000 persons in 209 villages and one town located to the west of Madras city, the town being 40 km from Madras. The entire resident population (except for children under 1 month old) was eligible for inclusion in the trial. Since it was considered that BCG vaccination might increase the specific immunity in people whose naturally acquired immunity (from virulent infection) might have waned in the course of time, persons classified as infected on the basis of the tuberculin test were not excluded from vaccination.

Study design : The design may be described as a 3×2 factorial, the first factor being the vaccine strain (and placebo), the second the dosage. For practical reasons only two seed lots—the French strain (seed lot 1173 P2) and the Danish strain (seed lot 1331)—were included in the trial and these were selected on the basis of their comparatively favourable effects in experimental models[19,20].

It should be noted that the French strain is in use in over 20 BCG production laboratories, and the Danish strain in several other laboratories, including the one in India. For the placebo preparation, dextran was freeze-dried in ampoules to form a powder of the same appearance as dried BCG vaccine. Since this preparation is innocuous, however, it does not cause the same kind of scar as BCG. The vaccine was administered at the usual strength (1 mg/ml) and one-tenth of this strength (0·1 mg/ml). The variations in dosage administered in most BCG vaccination programmes, including those due to variations in the viability of the vaccine and in the amount injected, have usually been well within this range.

Vaccines and placebo preparation : Three shipments of vaccines and placebo were

pplied by the State Serum Institute, openhagen, and three batches were supied by the BCG Vaccine Laboratory, uindy, Madras. The ampoules (10 ml Copenhagen, 5 ml in Madras) were icked in boxes of three. Each (coded) x contained 1 ampoule of strong vacne, 1 ampoule of weak vaccine of the me strain, and 1 ampoule of placebo, e ampoules in each box were randomly ded (1, 2, and 3), and the codes were pt in the production laboratories, by HO in Geneva, and by ICMR in New elhi; they were not available to the proct staff.

take: The intake was started in July '68 and completed in March 1971. e intake procedure consisted of a mplete house-to-house census to cord each person's name, relationship the head of the household, age, sex, cupation, etc. After the census, the rsons were directed to a conveniently cated examination centre. At this ntre, the identification was verified and e person's left shoulder was examined r the presence of a BCG scar. Persons ed 1 year or more were tested with 3 IU PPD-S and 10 'units' of PPD-B ntracellularin) and the reactions were ad in most cases after 72 hr. Subjects er 1 month old were vaccinated by tradermal injection of 0·1 ml of vaccine r placebo), after which a fingerprint r for small children a palmprint) was ken. X-ray examination was offered to ll persons aged 10 years or more and e X-ray films were examined independently by two readers. If on the basis f X-ray reading tuberculosis was suspect-, 'on the spot' and 'overnight' sputum mples were collected. The samples were amined by fluorescence microscopy and, after decontamination and concentration, were cultured on two Löwenstein-Jensen slopes. Cultures were classified as *Mycobacterium tuberculosis* on the basis of both the morphological characteristics of the colonies, the niacin test and other identification tests, such as growth characteristics at 25°C and drug sensitivity to 4-nitrobenzoic acid. The presence of drug resistance to isoniazid and streptomycin was also examined in all cultures.

Follow-up: The survey methods used at the time of intake were repeated at 2½-year intervals; X-ray examination being offered to all subjects 5 years of age and over. During the second resurvey (*i.e.* between 2½ and 5 years after intake), only those persons with reactions to PPD-S of less than 16 mm at intake and those considered at high risk in view of the previous examinations were examined. However, in a random sample of one-third of all villages included in the study, all individuals aged 5 years and above were examined at each resurvey according to the criteria adopted for the first resurvey.

Two or three times between surveys every village was visited and all persons who had had a suspect X-ray shadow at the previous survey, or who were absent at the previous survey, were offered X-ray examination. Also persons with cough or chest pain were invited to submit to an examination. A tuberculosis clinic was set up in the central town, and an X-ray unit visited the ten rural health institutions in the study area every 2-4 weeks. The diagnostic procedures were the same as during the intake. Cases diagnosed were offered domiciliary chemotherapy.

A 2 per cent random sample of the population was retested at 2½ months,

another 5 per cent were retested at 2½ years, and a further 85 per cent were retested at 4 years after vaccination. Retests were done with 3 IU of PPD-S only.

Results

Prevalence of infection and disease: The main findings of the intake examinations are summarized in Table 1. The calssification of the study population as infected or noninfected on the basis of PPD-S and PPD-B testing proved impossible[21]. The distribution of reaction sizes to PPD-S, however, showed a fairly clear antimode, in the lower age groups, at around 12 mm (Fig. 1) and persons with a reaction of 12 mm or larger may therefore be considered positive (infected). Indeed, among over 1000 patients with at least two positive cultures ,only 1·4 per cent had reactions to PPD-S smaller than 12 mm. At the chosen threshold, therefore, the test may be considered as highly sensitive. Those with reactions of 0-7 mm at intake have been considered as *definitely* not infected.

The sputum samples collected were examined by smear (fluorescence microscopy) and by culture. In comparison with culture, the smear examination appeared inferior, especially for the samples that showed scanty growth on culture: one-third of the patients were positive on culture only. On the other hand, 22 per cent of the patients were positive on smear only, but on most specimens only 1-3 bacilli were seen on the entire smear, and almost always only one of the smears was positive in this way. Whether such cases positive on smear only can be considered as bacillary cases, is doubtful. Therefore, only the culture results have been considered pathognomonic.

A high proportion of the patients were culture-positive on one specimens only. In these cases there were very often only a few colonies. While there must have been many true bacteriologically positive (perhaps early) cases of tuberculosis among these, some false cases (for example, contaminated samples) may have been included. Reproducibility of cultures as well as confirmation by other techniques was distinctly higher among cases positive on both culture and smear, than among cases positive on culture only. Cases positive on one culture only had certain features that were markedly different from those positive on two or more cultures. For this reason, the results are presented separately for those culture positive on two specimens and on one specimen.

As regards the X-ray examination, the agreement between the readers on active tuberculosis being possible or probable was not more than 47 per cent. A third reader examined all the cases so classified by one reader only. Only cases confirmed by two of the three readers are included in the figures given (Table I).

Incidence of infection and disease: Repeat tuberculin tests were given to assess the post-vaccination tuberculin sensitivity at 2½ months, 2½ years, and 4 years after intake. At 4 years, the sample was the largest and, especially for the 1-4 year age group, the observed incidence of infection in the control group makes it possible to estimate the risk of infection during this period (Table III). A person was considered to be newly infected if he was

Characteristics	Sex	Age (years) 0—4**	5—14	15—24	25—34	35—44	45—54	55—64	65+	Total
Population registered	M	24 074	46 494	29 905	28 384	22 161	16 691	10 467	6 093	184 269
	F	23 880	43 773	31 585	28 999	21 040	16 014	9 887	5 372	180 550
Completed intake examination* and vaccination	M	16 199	38 369	21 289	19 519	15 700	12 238	7 739	3 959	135 012
	F	16 136	36 093	19 988	20 259	16 336	12 088	6 749	2 511	130 160
Tuberculin positive (%) (>12 mm to 3 IU of PPD-S)	M	4·9†	23·5	62·0	81·8	85·2	85·5	82·6	79·9	54·0
	F	5·3†	21·3	48·4	64·0	71·6	73·7	72·3	72·8	45·8
Culture positive (per 10,000) (on 2 specimens)	M		1‡	33	115	179	213	219	201	111
	F		2‡	11	24	40	39	38	28	23
Culture positive (per 10 000) (one specimen only)	M		3‡	15	39	91	108	145	192	60
	F		2‡	10	17	29	42	40	39	20
Culture negative, but X-ray indicating active tuberculosis possible or probable (per 10 000)	M		31‡	47	107	245	379	478	703	189
	F		34‡	34	62	111	160	262	435	98

*Including children under 10 years of age, who were not eligible for X-ray examination and children under one year of age, who were not eligible for tuberculin test.

**Children less than one month old are excluded.

† 1— 4 years.

‡ 10—14 years.

Table II. Culture positive cases found during the first follow-up by age, tuberculin reaction, and X-ray result at intake

Intake examination: Tuberculin reaction (mm)	X-ray result	Age at intake (years) 0—4	5—14	15—24	25—34	35—44	45—54	55—64	65+	Total
Culture positive on at least two specimens										
0— 7	Normal	4	2	2	4	1	1	2	1	17
	Other			1		2		2	1	6
8—11	Normal			2	4	3				9
	Other				1		2	2	2	7
12—15	Normal		1	1	6	5	7	2	1	23
	Other			1	?	10	11	4	6	34
16+	Normal	1	10	37	51	63	4[illegible]	28	12	250
	Other		2	30	80	140	150	106	54	562
Total	*Normal*	5	13	42	65	72	56	32	14	299
	Other		2	32	83	152	163	114	63	609
Culture positive on one specimen										
0— 7	Normal	4	9	1	1[illegible]	1		1	2	19
	Other		2	1	1	3	2		1	10
8—11	Normal				1			1	1	3
	Other								2	2
12—15	Normal			3	2	2	1	1	3	12
	Other			1	?	1	1	4	4	16
16+	Normal		5	17	32	17	2[illegible]	15	7	113
	Other		1	16	38	53	58	52	30	248
Total	*Normal*	4	14	21	33	20	21	17	14	146
	Other		3	18	42	57	64	57	36	277

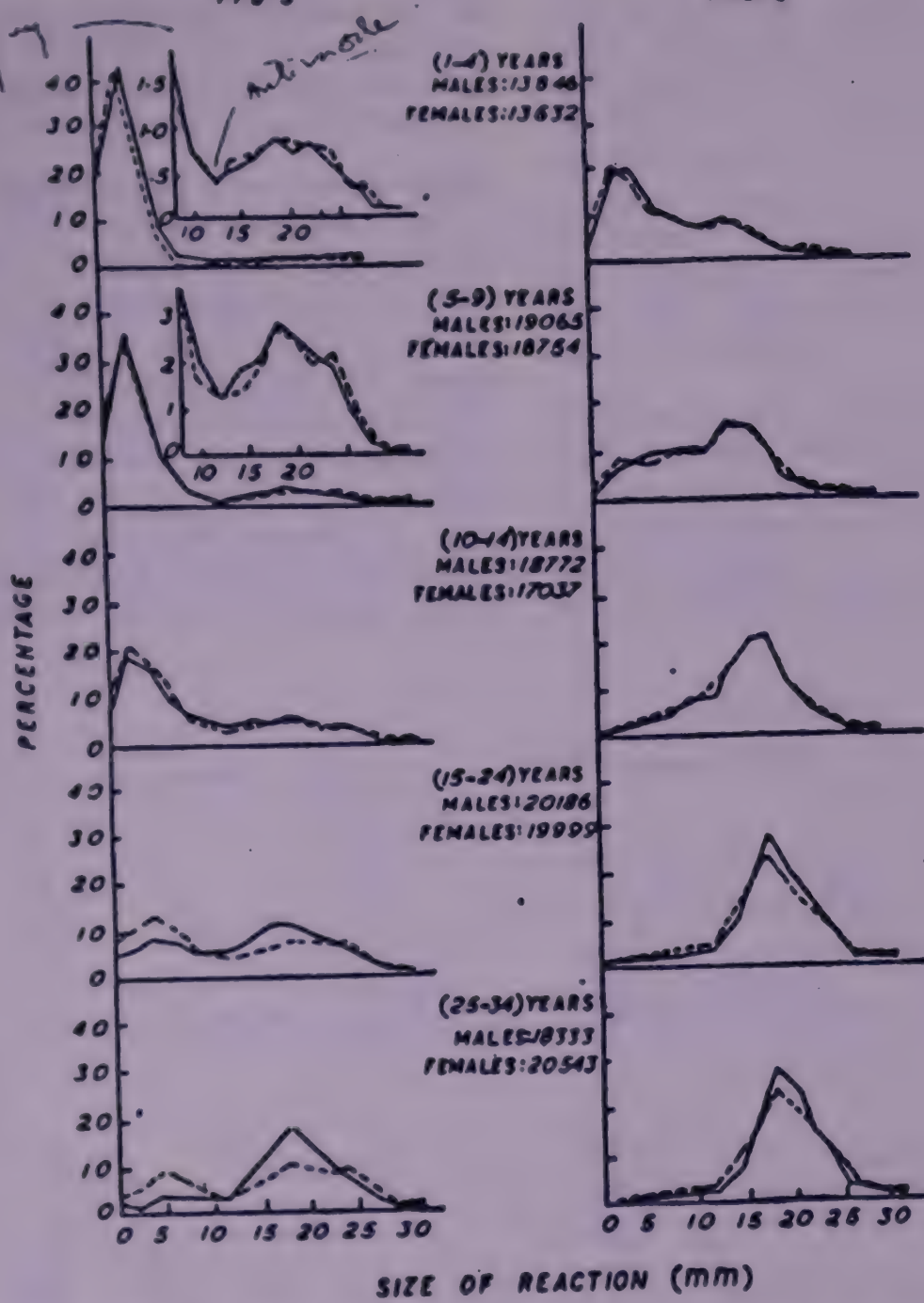


Fig. 1. Reactions to PPD-S and to PPD-B in the lower age groups at the intake. ———, Males; - - - - - - - -, Females.

infected at tintake (0-7 mm to 3 IU of D-S) and if his reaction to the same t was at least 10 mm larger 4 years er. The average annual risk of infection

Although the study population was large, these estimates must be considered as rough indications only, since in the population concerned the test used was not

Table III. Incidence and risk of infection in the [redacted] group during the first four years

	Age group (years)		
	1—4	5—9	10—14
No. with reaction of 0-7 mm at intake	4518	5467	3231
No. with ⩾10 mm larger reaction after 4 years	486	908	690
Average annual risk of infection (%)	2·8	4·4	5·8

Table IV. New cases with at least two culture-positive specimens and with one only (in brackets) detected during 7½ years of follow-up according to initial tuberculin reaction and vaccine group

Tuberculin reaction at intake (mm)	Vaccine (0·1 mg)	Vaccine (0·01 mg)	Placebo	Total
0— 7	37 (22)	37 (28)	28 (19)	102 (69)
8—11	14 (4)	17 (3)	14 (5)	45 (12)
12—15	40 (20)	34 (13)	38 (8)	112 (41)
•16+	259 (90)	257 (91)	287 (82)	803 (263)

•This complete group was not eligible for active follow-up during 2nd and 3rd resurveys.

tion with *M. tuberculosis* in the trial area appears to have been at least as common as in other parts of India, if not more so.

The incidence of pulmonary tuberculosis confirmed by culture during the first follow-up round is given in Table II. Relative to the population examined at intake, the average annual incidence of disease was 3 per 1000 in males and 1 per 1000 in females. Of particular interest in connection with the effect of BCG vaccination is the distribution of the cases found according to the tuberculin reaction at intake. Among those with a reaction of 0-7 mm the average annual incidence of cases positive on at least one specimen was 0·2 per 1000, among those with a reaction of 8-11 mm 0·4 per 1000, among those with 12-15 mm 1·5 per 1000, and among those with a reaction of 16 mm or more 4·5 per 1000. Thus, in those who were most probably not infected at intake the incidence of disease was surprisingly low (even when considering that two-thirds were vaccinated; vide Table IV).

BCG-induced tuberculin sensitivity : The level of tuberculin sensitivity induced by

BCG vaccination is an indication of the quality of the vaccination since this level is known to be correlated with the dose of (live) vaccine actually introduced into the skin[22]. Moreover, tuberculin sensitivity, as it reflects cell-mediated immunity, may be related to the protection afforded[23].

It appeared that there were no significant differences between the various batches of vaccine used. The observations in the age groups 0-4 and 5-9 years (at intake) for all the strong vaccines are therefore compared with the placebo (Fig. 2) to illustrate the level of tuberculin sensitivity induced and its development with time. At 2½ months after vaccination, the vaccinated persons in both groups showed a unimodal, almost normal distribution with a mean reaction size of 16·0 mm. After 2½ and 4 years this pattern had changed considerably and the reactions were much smaller. Still, the average level of sensitivity remained considerably higher than in the control group. Tuberculin sensitivity apparently waned during the first few years following vaccination but then remained at the same level. It should be noted that in this evaluation any boosting of tuberculin sensitivity as a result of repeated testing[24] was avoided by testing different sample populations on each occasion.

Incidence of tuberculosis among the vaccinated and the controls : The numbers of new cases detected during the first 7½ years of the follow-up, separately for the vaccinated and the control groups and for different levels of tuberculin (PPD-S) sensitivity at intake, are given in Table IV. Exact relative incidence figures are not yet available, but it may be taken that the denominators for the vaccine groups and the placebo group are the same. Thus it is clear at a glance that BCG vaccination at this stage had had no effect. Under these circumstances, the significance of the differences between vaccine strains and dosages can scarcely be examined. The very remote possibility of one strain being associated with a protective and the other with a harmful effect was examined. As no such difference was observed the results for both strains have been combined.

It is seen that in all groups the large majority of the cases occurred among those already infected at intake. In this connection it should be noted that those with a reaction of 16 mm or larger in all villages were not eligible for active follow-up during the later rounds. (For this reason column totals have been omitted).

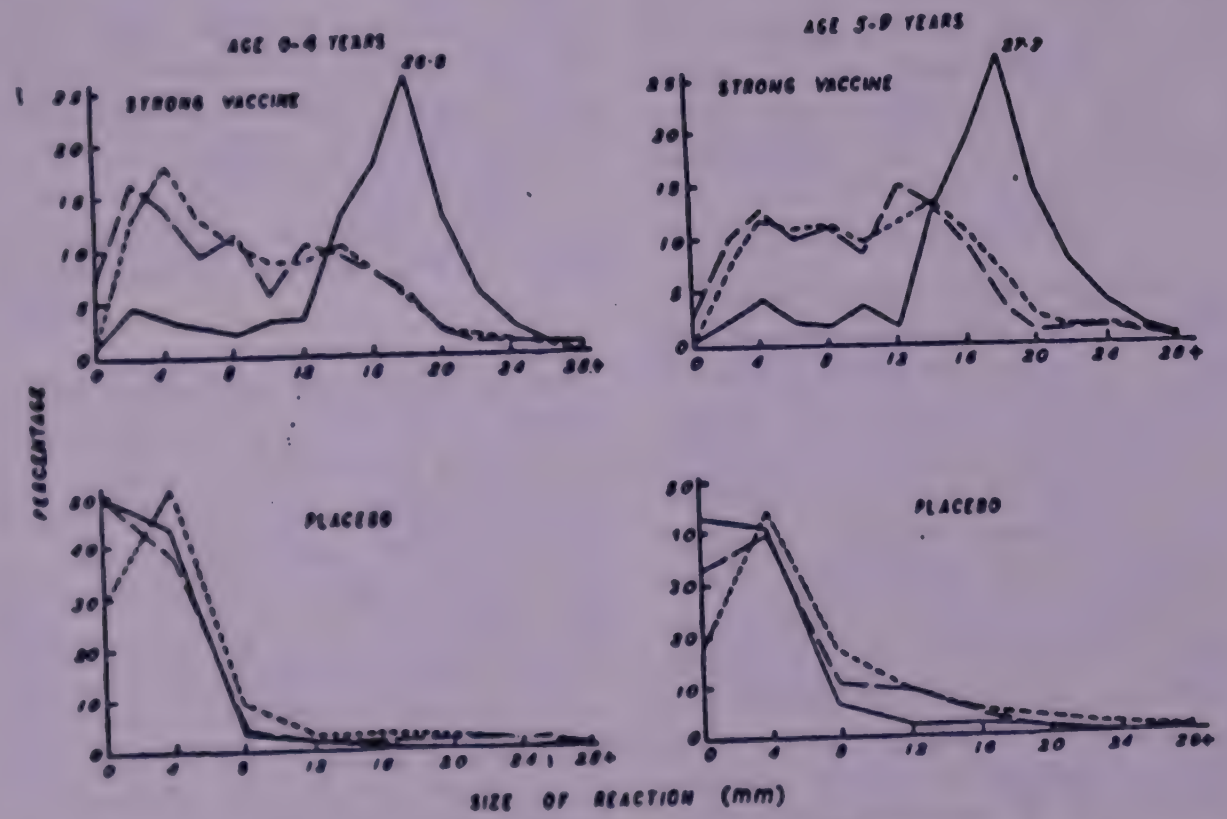


Fig. 2. Tuberculin reactions at various intervals after vaccination in persons with initial reactions of 0-7 mm. ————, At 2½ months; — — — — —, At 2½ years; · · · · · · At 4 years.

Discussion

The results of the trial reported here show that BCG did not give any protection during the first 7½ years after vaccination. Details of eight BCG trials, including the present one, in which the protection observed varied from 0 to 80 per cent, are given in Table V. BCG vaccination has been the subject of controversy throughout its more than 50-year history. With this new result at hand, it is perhaps appropriate to discuss some of the hypotheses that may explain the different findings.

There is no doubt that BCG strains mutate in terms of colony morphology and in terms of antigenicity. However, at least for the Danish strain, the evidence indicates that the vaccine strains used in these studies had not mutated from the original protective strains. The Danish strain used in India was the same as that used earlier in Britain[12], which did give substantial protection, and three circumstances favour the hypothesis that there was not any genetic change in the strain between 1952 and 1960 (when the strain was made into a stable seed-lot). First, every year for the last 30 years, the allergenicity of the Danish vaccine has been monitored in Danish school children and there has not been any change over this

Table V. Protection obtained in eight BCG trials

Trial and subjects	Duration of observation (years)	Percentage protection	Reference
North American Indians	9—11	80	25
Chicago : infants	12—23	75	11
Georgia : school children	20	None	8
Puerto Rico : population below 20 years	5½—7½	31	26
Georgia and Alabama : general population	14	14	10
Great Britain : school children	15	78	12
Madanapalle, South India: general population	9—14	31	27
Chingleput, South India : general population	7½	None	Present trial

period. Second, the methods used to propagate this strain between 1947 and 1960 were conservative, as advocated by Calmette. Third, comparison of vaccines prepared from the seed-lot with vaccines prepared from cultures maintained by culture transfers from 1958 to 1965, did not reveal any differences in morphology, antigenicity, or virulence in animals, or in allergenicity in children. For the French strain, the evidence is less clear. There was a mutation in pigmentation in the late 1950s though the French workers feel that they succeeded in saving the original strain by back-selection. In the recent experiment by D.W. Smith and coworkers (personal communication, 1979), the French strain protected guinea-pigs well, though significantly less than did the Danish strain. Further evidence on this point would be welcome. Thus, there is circumstantial evidence that the strains used here were 'genuine' BCG. A meeting of chiefs of quality control laboratories, held in Copenhagen in February 1978, concluded that the vaccines used in the trial were of good quality.

The methods and materials of the study were scrutinized at a meeting of experts held in Madras in 1977, and it was concluded that there were not any apparent flaws in the procedures followed in the study. With the very involved code for vaccine ampoules it is conceivable that true protection might have been masked by labelling or recording errors. However, since a blind reading of vaccination lesions in a very large proportion of population tallied with the records of the codes in 99·8 per cent of cases, such recording errors cannot have influenced the results.

Since the trial was carried out in an area with a high prevalence of nonspecific sensitivity, it might be expected that sensitization by 'atypical' mycobacteria would result in an apparent reduction of the effect of BCG. Had some protection been observed in the present trial, this question could have been examined; with zero protection this was not possible. However, the hypothesis has once been tested, retrospectively: in the study in Puerto Rico, vaccine and placebo were allocated irrespective of the reaction to a high-dose test, and it turned out that there was the same low protection (31 per cent) in those positive and those negative to the high-dose test[17,28].

It could be hypothesized that the lack of protection observed in this study may be due to the vaccinated individuals being at increased risk of developing tuberculosis if they were infected within 8 weeks after vaccination, *i.e.* before the manifestation of cell-mediated immunity. This, however, is unlikely and is not borne out by the findings.

Vaccines similar to the ones used in the present study have given a high protection in some (though not necessarily all) past studies. Our forecast of the incidence of tuberculosis among persons tuberculin-negative at the time of vaccination was based on available knowledge of tuberculosis epidemiology, and in particular, on the results of the 'longitudinal survey' conducted from 1960 onwards in Bangalore district, Karnataka, by the National Tuberculosis Institute[29]. During the first resurvey of that study, after 18 months, the annual incidence of new bacillary cases among those with a reaction of 0-9 mm to RT 23 (1 unit, with Tween 80) was estimated at 58 per 100 000 while in the present study among those reacting with 0-7 mm to PPD-S 3IU, it was only 25 per 100 000. Though the data are not strictly comparable, the very much lower risk among non-reactors in the present study in relation to the considerably higher risk among those defined as infected at intake, is a very striking finding.

It appears, therefore, that while the infection rate is high in this study population and possibly not declining, newly infected persons develop disease less frequently. Tuberculosis is highly prevalent, but only among the middle-aged and especially elderly men, individuals who must have been infected many years, even decades, ago. It is possible that it is not the primary infection but rather superinfection in the host already allergic from a previous infection that is the cause of the 'adult' type of lung tuberculosis. Could it be that BCG protects against endogenous reactivation but not against exogenous re-infection? This requires further investigation.

A local phenomenon that may be of relevance is the frequency of strains of *M. tuberculosis* that are of very low virulence in the guineapig. This phenomenon was exhaustively studied by Mitchison[30]. Mitchison found these low-virulence strains to be susceptible to hydrogen peroxide, though they tended to be catalase-positive. Nothing seems to be known, however, about the epidemiological significance of these strains. They have been isolated from previously untreated patients admitted to the Tuberculosis Chemotherapy Centre, Madras (so they are presumbly not always avirulent in man), and they were niacin-positive and isoniazid-sensitive. Strains from elsewhere in India is scanty but compatible with the existence of these low-virulence strains in other parts of the country. Work is now underway in this project to study the distribution of such strains, especially in regard to age distribution, infection history, and fate of the patients. While there is as yet no indication of an association between the prevalence of these strains and the BCG results, it nevertheless seems worthwhile to investigate this phenomenon.

In conclusion, the present study has revealed that BCG did not show any protection against the development of bacillary disease. Protection afforded to individuals against the development of active disease other than bacillary forms remains to be studied. It should be pointed out that the present results may not be extrapolated to infants, since infant tuberculosis was not observed in the trial. Information on the effect of BCG vaccination in infants is scarce, and additional data are badly needed.

References

1. ten Dam, H.G., Toman, K., Hitze, K.L. and Guld, J. Present knowledge of immunization against tuberculosis. *Bull WHO* 54 (1976) 255.
2. Frappier, A., Portelance, V., St-Pierre, J. and Panisset, M. BCG strains: Characteristics and relative efficacy. In: *Status of Immunization in Tuberculosis in 1971*. Ed. E.C. Chamberlayne, (DHEW publication No. NIH 72-68) 1971, p 157.
3. Dubos, R.J. and Pierce, C.H. Differential characteristics in vitro and in vivo of several substrains of BCG. *Am Rev Tub Pulm Dis* 74 (1956) 699.
4. Willis, H.S., Vandiviere, H.M., Vandiviere, M.R. and Melvin, I. Studies in tuberculo-

Willis, H.S. and Vandiviere, M.R. The heterogeneity of BCG. *Am Rev Respir Dis* 84 (1961) 288.

Jespersen, A. *The Potency of BCG Determined on Animals. Copenhagen Statens Seruminstitut*, 1971.

Hart, P. D'Arcy, Sutherland, I. and Thomas, J. The immunity conferred by effective BCG and vole bacillus vaccines, in relation to individual variations in induced tuberculin sensitivity and to technical variations in the vaccines. *Tubercle* 48 (1967) 201.

Comstock, G.W. and Webster, R.G. Tuberculosis studies in Muscogee County, Georgia. *Am Rev Respir Dis* 100 (1969) 839.

Bettag, O.L., Kaluzny, A.A., Morse, D. and Radner, D.B. BCG study at a state school for mentally retarded. *Dis Chest* 45 (1964) 503.

Comstock, G.W. and Palmer, C.E. Long-term results of BCG vaccination in the southern United States. *Am Rev Respir Dis* 93 (1966) 171.

Rosenthal, S.R., Loewinsohn. E., Graham, M.L., Liveright, D., Thorne, M.G. and Johnson, V. BCG vaccination against tuberculosis in Chicago. A twenty year study statistically analyzed. *Pediatrics* 28 (1961) 622.

British Medical Research Council. BCG and Vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. *Bull WHO* 46 (1972) 371.

Youmans, G.P., Parlett, R.C. and Youmans, A.S. The significance of the response of mice to immunisation with viable unclassified mycobacteria. *Am Rev Respir Dis* 83 (1961) 903.

Palmer, C.E. and Long, M.W. Effects of infection with atypical mycobacteria on BCG vaccination and tuberculosis. *Am Rev Respir Dis* 94 (1966) 553.

Edwards, L.B. and Palmer, C.E. Identification of the tuberculous-infected by skin tests. *Ann NY Acad Sci* 154 (1968) 140.

16. Hart, P. D'Arcy. Efficacy and applicability of mass BCG vaccination in tuberculosis control. *Br Med J* 1 (1967) 587.

17. Comstock, G.W. and Edwards, P.Q. An American view or BCG vaccination, illustrated by results of a controlled trial in Puerto Rico. *Scand J Respir Dis* 53 (1972) 207.

18. WHO Expert Committee on Biological Standardization. Eighteenth Report. *WHO Tech Rep Ser* 329 (1966).

19. Vallishayee, R.S., Shashidhara, A.N., Bunch-christensen, K. and Guld, J. Tuberculin sensitivity and skin lesions in children after vaccination with 11 different BCG strains. *Bull WHO* 51 (1974) 489.

20. Ladefoged, A., Bunch-christensen, K. and Guld, J. Tuberculin sensitivity in guinea-pigs after vaccination with varying doses of BCG of 12 different strains. *Bull WHO* 53 (1976) 435.

21. Raj Narain, Vallishayee, R.S. and Venkatesha Reddy, A. Value of dual testing with PPD-S and PPD-B. *Indian J Med Res* 68 (1978) 204.

22. Edwards, L.B., Palmer, C.E. and Magnus, K. BCG vaccination, Geneva. *WHO Monogr Ser* 12 (1953).

23. Mackaness, G.B. The immunology of anti-tuberculous immunity. *Am Rev Respir Dis* 97 (1968) 337.

24. Guld, J., Waaler, H., Sundaresan, T.K., Kaufmann, P.C. and Ten Dam, H.G. The duration of BCG-induced tuberculin sensitivity in children and its irrelevance for re-vaccination. *Bull WHO* 39 (1968) 829.

25. Stein, S.C. and Aronson, J.D. The occurrence of pulmonary lesions in BCG-vaccinated and unvaccinated persons. *Am Rev Tub Pulm Dis* 68 (1953) 695.

26. Palmer, C.E., Shaw, L.A. and Comstock, G.W. Community trials of BCG vaccination. *Am Rev Tub Pulm Dis* 77 (1958) 877.

27. Frimodt Moller, J., Acharyulu, G.S. and Parthasarathy, R. Observations on the protective effect of BCG vaccination in a South Indian rural population. *Indian J Tub* 15 (1968) 40.

28. Comstock, G.W., Livesay, V.T. and Woolpert, S.F. Evaluation of BCG vaccination among Puerto Rican children. *Am J Public Health* 64 (1974) 283.

29. National Tuberculosis Institute, Bangalore. Tuberculosis in a rural population of South India : a five-year epidemiological study. *Bull WHO* 51 (1974) 473.

30. Mitchison, D.A. The virulence of tubercle bacilli from patients with pulmonary tuberculosis in India and other countries. *Bull Int Un Tubere* 35 (1964) 287.

Reprint requests : Dr. G.V.J. Baily, Project Director, Tuberculosis Prevention Trial, Spurtank Road, Chetput, Madras-600031.

231/81

Br. J. Dis. Chest (1980) 74, 215

(3)

EFFECTIVENESS OF BCG VACCINATION IN GREAT BRITAIN IN 1978

A Report from the Research Committee of the British Thoracic Association*

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE LIBRARY 8 DEC 1980

Summary

BCG vaccination of older school-children in Britain continues to offer more than 70% protection against tuberculosis for at least ten years after vaccination.

In England and Wales between 1973 and 1978 the tuberculosis notification rate in tuberculin-negative unvaccinated life-time residents aged 15–19 years fell by 50%. There was no change in rate for those given BCG vaccination, possibly because of less satisfactory techniques of vaccination in some areas.

It is estimated that for life-time residents of England and Wales BCG vaccination of 100 000 older school-children in 1978 will prevent about 44 notifications in the 15 years following vaccination.

Introduction

Previous studies have given evidence of the protective effect of BCG vaccination in adolescents in England and Wales, both in a controlled trial (Hart & Sutherland 1977) and in routine use (British Thoracic and Tuberculosis Association 1975). Because of the decline in annual infection risk indicated by a tuberculin survey (Christie & Sutherland 1976) the possibility has been considered that the time might be approaching when the national policy of routine BCG vaccination for all older school-children (aged 10–13 years) should be reviewed (Stilwell 1976; Springett 1976). This paper provides further estimates of the contribution made by the schools BCG scheme in recent years, but does not attempt to formulate policy.

In addition to ascertaining the present effectiveness of BCG vaccination given under routine conditions, the present study has two further objectives. One is to measure the effectiveness of BCG over a longer period after vaccination than in the British Thoracic and Tuberculosis Association study in 1973 (published in 1975). The other is to test the hypothesis that tuberculosis due to recent infection is declining at about the same rate as has been shown for the annual risk of infection. The opportunity was also taken to extend the survey area to the whole of Britain by including Scotland as well as England and Wales.

To achieve the first of these objectives the age range covered in 1978 was extended from 15–19 years as in 1973 to 15–24 years. As a result the group studied at age 20–24

*The survey was carried out by a subcommittee of the Research Committee of the British Thoracic Association, whose members were: J. H. Angel (*Chairman*), V. H. Springett (*Coordinator*), C. A. C. Pickering and I. Sutherland. The report was prepared by V. H. Springett and I. Sutherland.

years in 1978 represents the same cohort as had been studied at age 15–19 years in 1973 hence the protective effect of vaccination can be studied in the cohort for a five-year period.

The second objective may be achieved, at least in part, by a comparison of notification rates of BCG-vaccinated and tuberculin-negative unvaccinated groups years in 1973 and 1978. The development of tuberculosis in these groups must depend closely on the risk of infection, and the change in the incidence of disease should therefore correspond approximately to the change in the risk of

Methods

The method was similar to that used in 1973. The cooperation of chest physicians throughout the country was first sought and a high proportion agreed to participate. They were asked to complete a survey form for each person in the 15–24 age group notified as suffering from TB of any site during 1978 and to return the form to the coordinator. In addition to particulars of identity and the localization of tuberculosis, the form was designed to record the tuberculin reaction with special reference to the schools BCG scheme; the result of the tuberculin test or of BCG vaccination was confirmed from contemporary records if possible. For those who had had BCG, information was also requested on the presence or absence of a scar at the vaccination site. For immigrants who first entered Britain when aged 15 years or more only the date of entry to Britain was required, since they could not have been included in the schools BCG scheme.

Some weeks after the end of each quarter of the year the coordinator received tables from the Office of Population Censuses and Surveys and from the Information Services Division of the Scottish Home and Health Department showing the number of notifications in the age groups for each sex, and for respiratory and non-respiratory tuberculosis for each administrative district. The number of survey forms received from each district was compared with the number in the table, and if necessary a reminder letter with further forms was sent to the chest physicians concerned.

At the end of the year, when the final total of notifications for each district was known, a list of names of the persons for whom forms had been received was sent to each chest physician to ask for information on the results of bacteriological investigations or any revision of diagnosis.

By relating the numbers of notifications in the various groups to the corresponding population (see below), notification rates were obtained or estimated for the BCG-vaccinated and the unvaccinated tuberculin-positive and tuberculin-negative groups.

Results

Population estimates

The tuberculosis notifications analysed in this report are those occurring among the population who were aged 15–24 years in 1978 and who had been resident in Great Britain at age 13 years (when BCG vaccination is offered in most schools). In some areas BCG is offered at a slightly younger age, but this is not of major importance. The relevant total population has been obtained from the Registrar General's estimates of the number of persons aged 13 years on 30 June each year from 1967 to 1976 (Office of Population Censuses and Surveys 1975, 1977, 1979). The population aged 15–24 years in 1978 resident since age 13 years, is thus estimated at 8080 000. No allowance has been made for death or emigration from Great Britain between age 13 years and 1978, because the numbers involved are not large and will not have materially altered the proportions in this population cohort according to skin test and vaccination status.

The subdivision of this total according to status at age 13 years in relation to the schools BCG vaccination scheme has been made as follows:

1. The local authority returns to the health departments for school-children and students show that 5630 000 were given BCG in the years 1967–76; this total includes a relatively small number of vaccinations of students at older ages, which cannot be separated, but does not include vaccinations of contacts. During the same period a further 639 000 were found to be tuberculin-positive and were not vaccinated.

2. The balance of 1811 000 ostensibly consists of non-participants in the scheme. However, they include a small number who were found to be tuberculin-negative in the scheme but were not vaccinated. Scrutiny of the detailed returns for England and Wales in 1976 suggests that the proportion of tuberculin-negative children escaping vaccination is close to 1%. This leads to an estimate of 57 000 found to be tuberculin-negative in the schools scheme but not vaccinated.

3. In addition, some of the non-participants will have been outside the scope of the scheme because they had already been found to be tuberculin-positive or had been given BCG before age 13 years, usually as contacts. The local authority returns of the numbers vaccinated as contacts are not subdivided by age, nor is there any routine record of the numbers of contacts found to be tuberculin-positive when tested. In the British Thoracic Association contact study (British Thoracic Association 1978), carried out in 37 chest clinics in Britain in 1973–4, 71% of 1156 unvaccinated close contacts with grade 0 or 1 Heaf test reactions were aged under 15 years, and 24% of 662 unvaccinated close contacts aged 5–14 years were found to have grade 2 or greater Heaf test reactions. On the basis of these figures it has been assumed that 75% of those vaccinated in Britain as contacts were under 13 years and that 25% of all the contacts tested under this age were tuberculin-positive. Applying these percentages to the total numbers vaccinated as contacts in the years 1967–76 from the local authority returns, those found to be tuberculin-positive prior to age 13 years are estimated to be 126 000 and those given BCG before age 13 years to be 379 000. After subtracting these two estimates (and the estimate in the previous paragraph) from the non-participants, there remain an estimated 1249 000 who, though eligible, did not participate in the scheme.

4. Finally, it has been assumed that the proportion of these non-participants who were tuberculin-positive was the same as among the participants in the scheme. This leads to estimated totals of 124 000 tuberculin-positive non-participants and 1125 000 tuberculin-negative non-participants in Great Britain. The accuracy of this assumption is surprisingly not of critical importance; even if the proportion of tuberculin-positives in non-participants is assumed to be twice that in participants the estimates of the effectiveness of BCG remain almost the same.

Population estimates on the same basis have been calculated separately for the two five-year age groups 15–19 and 20–24 and also separately for England and Wales.

Notifications

Table I shows that the survey forms were received for 1269 (77.5%) of the 1638 persons aged 15–24 years notified as suffering from tuberculosis in Great Britain in 1978. The proportion of forms received was similar for Scotland (79.5%) and for both the 15–19 year age group (78.3%) and the 20–24 year age group (76.7%) in England and Wales.

The proportion of forms received was lower for non-respiratory tuberculosis (60%) than for respiratory tuberculosis (85%).

There were 648 forms for immigrants who entered this country after the age at which BCG is given in most schools and they had not therefore been available to take part in the scheme. The proportion of immigrants entering after school age was much lower for Scotland (8%) than for England and Wales, where the proportion was lower (35%) in the 15–19 year age group than in the 20–24 year age group (66%).

Also shown in Table I is a total of 72 who had not been eligible for the schools BCG scheme because of events before the usual age for vaccination. Six had had tuberculosis, 27 had had a positive tuberculin test and 39 had had BCG vaccination.

Table I. Great Britain 1978, persons aged 15–24 years. Notifications of tuberculosis and survey forms received

Notifications of tuberculosis		1638	
Survey forms received		1269	(77.5%)
Eligible for schools BCG scheme		511	
BCG vaccinated	212		
Tuberculin +ve	109		
Non-participant	190*		
Not eligible for schools BCG scheme		720	
Tuberculosis, tuberculin +ve or BCG *before* age 13 years	72		
Immigration *after* age 13 years	648		
Wrong age, year or diagnosis, and duplicate notifications		38	

*Includes ten found tuberculin-negative but not vaccinated.

There were an additional 38 forms which were not included in the main analysis, nine because the original diagnosis of tuberculosis had been revised, eight because they represented duplicate notifications and 21 because of errors of classification of age or of year of notification.

There remain 511 forms for persons who had been eligible for the schools BCG scheme: 212 had received BCG vaccination, 109 had been found tuberculin-positive and 190 had not participated in the scheme, including ten who had had a negative tuberculin test but had not had BCG vaccination. Table II summarizes some features of these three groups.

The fact of BCG vaccination was confirmed from the original records for 61%. In those aged 15–19 years confirmation was obtained for 79%, but in those aged 20–24 years confirmation was possible for only 45%, mainly because of the destruction of the records at varying intervals after school-leaving age. A scar at the site of vaccination was recorded for 90%, no report being made for most of the remainder.

The proportion with confirmation of a positive skin test is higher at 75% and again the proportion confirmed from the records is greater in the younger age group, 83% compared with 58%. The higher proportion confirmed in positives is probably related to the fact that in many areas positive results are reported to the chest clinic, where the record is held for longer than in the immunization records.

The proportion of the non-participants in whom it could be confirmed that BCG had not been administered is much lower, mainly because of the inherent difficulty of confirming a non-event. Confirmation was possible only in special circumstances, such as active refusal of permission by the parent. The more common reasons such as absence from school (which may have been intentional) were not confirmed.

Table II. Comparison of survey groups

	Classification in schools BCG scheme					
	BCG vaccinated		Tuberculin +ve		Non-participant	
	No.	%	No.	%	No.	%
Total	212	100.0	109	100.0	190*	100.0
Classification in schools scheme confirmed from original record	130	61.3	82	75.2	35	18.4
Not confirmed, BCG scar	62	29.2	—		—	
Not confirmed, no scar	20	9.4	—		—	
Tuberculosis confirmed by bacteriology or histology	107	50.5	52	47.7	78	41.1
Negative bacteriology	49	23.1	36	33.0	66	34.8
No information on bacteriology	56	26.4	21	19.3	46	24.2
Born in						
Great Britain	163	76.9	53	48.6	146	76.8
Asia or Africa	38	17.9	52	47.7	30	15.8
Rest of world	11	5.2	4	3.7	14	7.4
Non-respiratory tuberculosis	30	14.2	22	20.2	15	7.9
Males	93	43.9	52	47.7	90	47.4
Females	119	56.1	57	52.3	100	52.6
Age 15–19 years	101	47.6	76	69.7	90	47.4
Age 20–24 years	111	52.4	33	30.3	100	52.6

*Includes ten found tuberculin-negative but not vaccinated.

Evidence of confirmation of the diagnosis of tuberculosis by bacteriological or histological findings was reported to the survey in less than half the cases. These low figures are partly due to the fact that results, even when available, were not always reported to the coordinator. The highest proportion of confirmed diagnoses was in the BCG-vaccinated group, which suggests that if anything this group may have been subjected to more stringent standards of diagnosis than the other groups.

Amongst this group of persons who were aged 15–24 years when notified in 1978 and who were resident in Great Britain when aged 13 years, the proportion of immigrants before the age of 13 years was much higher in the tuberculin-positive group (51%) than in the BCG vaccinated group (23%) or the non-participants (23%). This larger proportion of immigrants among the patients most probably reflects a larger proportion of

immigrants in the relatively small tuberculin-positive population than in the vaccinated and non-participant populations.

Non-respiratory tuberculosis occurred in a higher proportion of patients who were tuberculin-positive than in the other two groups, probably because of the higher proportion of immigrants in this group. In all groups there were slightly more notifications of females than of males.

In the BCG vaccinated and non-participant groups just under half the notifications were in the 15–19 year age group, with a slightly larger number at age 20–24 years. In contrast to this there were many more notifications at age 15–19 years than at age 20–24 years in the tuberculin-positive group. This reflects the relatively high incidence in the first few years after primary infection in the 15–19 year age group, whereas the 20–24 year age group are known to have been positive for at least seven years.

Table III. Great Britain 1978. Persons age 15–24 years. Estimation of notification rates in survey groups

Classification in schools BCG scheme	*Population* (*a*)	*Survey returns* (*b*)	*Notification rate* (per 100 000) $c = \frac{b}{a} \times 100\,000$	$d = c \times \frac{100}{77.5}$
BCG-vaccinated	5630 000	212	3.77	4.86
Tuberculin-positive	639 000	109	17.06	22.01
Non-participant, not previously tuberculin-positive or vaccinated	1249 000	180	—	—
Estimated tuberculin-positive	124 000	21.2	17.06	—
Estimated tuberculin-negative	1125 000	158.8	—	—
Tuberculin-negative, not vaccinated	57 000	10	—	—
All negative not vaccinated	1182 000	168.8	14.28	18.43
Protective effectiveness				74%

c—based upon reported notifications.
d—corrected to allow for under-reporting (see text).

Notification rates

From the population given BCG vaccination and the number of notifications in the BCG vaccinated group a notification rate can be calculated for BCG vaccinated subjects, as shown in the first line of Table III. The rate (*c* in Table III) based on notifications reported to the survey is 3.77 per 100 000, and this is multiplied by 100/77.5 to allow for under-reporting to give a rate (*d* in Table III) representing all the notifications in Great Britain in vaccinated subjects of 4.86 per 100 000.

The notification rate for those found to be tuberculin-positive at school can also be calculated directly. As shown in line 2 of Table III it is 17.06 per 100 000 for notifications reported to the survey, increased to 22.01 per 100 000 when allowance is made for under-reporting.

A rate for all non-participants could be calculated similarly, but is of little interest. The population of non-participants has been divided into tuberculin-positives and tuberculin-negatives on the assumption that they occur in the same proportion as in

the tuberculin tested participant group. (As explained above, this is not a critical assumption.) If it is further assumed that the notification rate observed in the tuberculin-positive group applies also to this estimated positive group, then the number of notifications in the group can be estimated. Subtracting this number from the total of notifications in non-participants gives the number of notifications in estimated tuberculin-negative non-participants and thus a rate for tuberculin-negative non-participants can be calculated after adding both population and cases for the small group found tuberculin-negative but not vaccinated. The rate so obtained for tuberculin-negatives is 14.28 per 100 000 or 18.43 after allowing for under-reporting.

Table IV. England and Wales. Estimated notification rates per 100 000 corrected for under-reporting

	1973	1978	
	Age 15–19	Age 15–19	Age 20–24
BCG vaccinated	3.7	3.8	5.2
Tuberculin-positive, not vaccinated	40.9	37.9	11.9
Tuberculin-negative, not vaccinated	28.5	12.3	21.8
No. of cases	243	211	198
Protective effectiveness	87%	69%	76%

Table V. Scotland 1978. Estimated notification rates per 100 000 corrected for under-reporting

	Age 15–19 *years*	*Age* 20–24 *years*
BCG vaccinated	8.3	7.8
Tuberculin-positive, not vaccinated	12.4	15.2
Tuberculin-negative, not vaccinated	35.9	65.2
No. of cases	39	40
Protective effectiveness	77%	88%

These calculations have also been carried out separately for the two five-year age groups, separating the results for England and Wales from those for Scotland. The results from the 1973 study of persons aged 15–19 years in England and Wales have been recalculated on the same basis, including the use of revised population estimates. The notification rates so obtained and corrected for under-reporting are shown for the three main survey groups in Table IV for England and Wales, and Table V for Scotland, but without showing all the steps of the calculation.

Notification rates for life-time residents of England and Wales

As indicated previously, the survey notifications for England and Wales include a substantial proportion (34%) of immigrants, a group in which the notification rate is

known to be much higher than in the rest of the population (British Thoracic and Tuberculosis Association 1973). Place of birth is recorded on the survey forms, so that the number of notifications of life-time residents of England and Wales can be counted separately.

From the 1971 Census estimates have been made of the population of life-time residents of England and Wales aged 13 years in the years 1967–76. By relating the corresponding survey notifications to this population, notification rates for life-time residents are obtained as shown in Table VI. The proportions given BCG, found tuberculin-positive and not participating are assumed to be the same in life-time residents as in the total population. In the population as a whole the proportion of immigrants before the age of 13 years is so small (4%) that the inaccuracies involved cannot seriously affect the estimate.

Table VI. England and Wales. Estimated notification rates per 100 000 life-time residents, corrected for under-reporting

	1973	1978	
	Age 15–19	Age 15–19	Age 20–24
BCG vaccinated	2.5	2.6	4.2
Tuberculin-positive, not vaccinated	17.7	14.1	7.6
Tuberculin-negative, not vaccinated	21.1	10.5	17.4
Number of cases	145	127	149
Protective effectiveness	88%	76%	76%

It is, however, impossible to make reliable estimates of the size of the immigrant population, or of the proportions who were vaccinated, found positive or did not participate in the schools BCG scheme. Therefore no attempt has been made to assess the effectiveness of BCG vaccination in immigrants.

Protective effectiveness

The protective effectiveness of BCG vaccination is the percentage reduction in notification rate in the BCG vaccinated group compared with the tuberculin-negative unvaccinated group. For the 15–24 age group in Great Britain, including immigrants before the age of 13 years, this is

$$\frac{100(18.43-4.86)}{18.43} = 74\% \text{ (Table III)}$$

In each sub-grouping by age, calendar year, geography or place of birth shown in Tables IV, V and VI the protective effectiveness is never below 69% and in two sub-groups is as high as 88%.

The protective effectiveness is at about the same level in Scotland as in England and Wales, though the number of cases for analysis is rather small. The protective effectiveness in England and Wales in the cohort aged 15–19 years in 1973 and 20–24 years in 1978 is only slightly affected by removing the immigrant population, but for the cohort

aged 15–19 years in 1978 the estimated protective effectiveness is increased from 69% to 76% if immigrants are excluded.

Discussion

This study has given two important results: first, that in the year 1978 the schools BCG vaccination scheme continued to give at least 69% protection in those aged 15–19 years who had been given BCG vaccination at school; secondly, that this level of protection is continued for at least a further five years from vaccination to cover the group aged 20–24 years in 1978.

The other main objective of this study was to assess changes in notification rates between 1973 and 1978, especially in the tuberculin-negative and BCG-vaccinated groups, as indicators of change in the infection rate. To achieve this, the actual rates in these groups must be compared in the two years. To make the comparison as precise as possible this needs to be done for life-time residents of England and Wales only; Scotland was not included in the 1973 study. The restriction to life-time residents is necessary because of the much higher notification rates in immigrants, as a result of which even relatively small changes in the proportion of immigrants could lead to appreciable changes in the rates under study.

For convenience, the rates in Scotland in 1978 are first compared with those in England and Wales. The changes in the rates in life-time residents of England and Wales between 1973 and 1978 are then considered.

Notification rates in Scotland and in England and Wales in 1978

For tuberculin-positives the notification rate in Scotland (which has few immigrants) (Table V) is similar to that in England and Wales (excluding immigrants) (Table VI) at age 15–19 years, but higher at age 20–24 years. In the BCG-vaccinated and tuberculin-negative groups the rates in Scotland are two or three times as great as in England and Wales (excluding immigrants). The pattern suggests that the infection risk is higher in Scotland than in England and Wales, and that it is at the level it was in England and Wales five to ten years earlier.

Notification rates in life-time residents of England and Wales in 1973 and 1978

The notification rates in Table VI are used as the basis for this discussion. The rates for the 15–19 age group in 1973, and hence the protective effectiveness, differ from those in the published report of the earlier study (British Thoracic and Tuberculosis Association 1975) because (*a*) immigrants have been excluded from both cases and populations and (*b*) allowance has been made in the population estimates for more recent information and for individuals vaccinated or found tuberculin-positive before age 13 years.

For those who are unvaccinated and *tuberculin-positive* at about age 13 years the notification rate at age 15–19 years in 1978 is 14.1 per 100 000, 20% lower than the rate of 17.7 per 100 000 in the same age group in 1973. This suggests that the general level of infection rate plays some part in influencing the notification rate in tuberculin-positives. The rate in the 20–24 age group in 1978 is substantially lower than in the

15–19 age group in either year, confirming the fall in rate at longer intervals from the positive test.

For those *tuberculin-negative* at about age 13 years the notification rate at age 15–19 years in 1978 is 10.5 per 100 000, 50% lower than the rate of 21.1 per 100 000 in the same age group in 1973. This decline is the same as the decline in infection risk that has been suggested from a tuberculin survey. In the 20–24 age group the rate of 17.4 per 100 000 in 1978 is below the rate of 21.1 per 100 000 recorded for the same cohort when aged 15–19 years in 1973.

For those *vaccinated with BCG* at about age 13 years the notification rate at age 15–19 years is 2.6 per 100 000 in 1978 and 2.5 per 100 000 in 1973. This negligible change in rate suggests either that there has been no decline in infection risk or that there is some other reason for the absence of a decline in this group. At age 20–24 years the rate of 4.2 per 100 000 in vaccinated subjects in 1978 is greater than the rate of 2.5 per 100 000 in the same cohort when aged 15–19 years in 1973.

Thus, the pattern in BCG-vaccinated subjects aged 15–19 years, in whom there has been no decline in notification rate, is quite different from that in tuberculin-negative subjects aged 15–19 years, in whom the rate has declined by 50% between 1973 and 1978. The methods adopted in the two studies were identical and the percentage response was similar. It is difficult to see how the difference in trends could be due to any differences in study procedures.

The notification rate in tuberculin-negatives has been assessed in the same way for each study, and they are not subject to any other procedure which could affect their rates, so that it is difficult to regard the decline as an artefact; the decline is unlikely to have arisen by chance ($P < 0.001$).

The absence of a similar decline in the BCG-vaccinated group could be due to changes in vaccination and related procedures in 1972-6 as compared with 1967–71. In many areas the Tine test has been introduced in recent years instead of the Heaf test. However, the recent British Thoracic Association study of the Tine test in comparison with the Mantoux test (Lunn & Johnson 1978) has cast doubt on the reliability of the Tine test in identifying those infected and its consistency in different hands. Further, from about 1972 there was a change in vaccination policy in many areas, children with Grade I reactions to the Heaf test now being vaccinated. The extent of these changes is unknown, but their effects will presumably have been similar. Both result in the transfer of a proportion of those with weak positive reactions from the tuberculin-positive to the vaccinated group. Those with weak positive reactions probably have some natural protection against the development of tuberculosis, and the expected incidence of tuberculosis among them, if they are not vaccinated, is low. The benefits of vaccination in this group are probably also small. The nett result of transferring even quite a large proportion of weak positive reactors to the vaccinated group would be a slight increase in rate in the tuberculin-positive group and no change or a slight increase in the BCG-vaccinated group. These two changes cannot resolve the anomaly.

The average viable bacterial count in the batches of BCG vaccine issued for use in Great Britain was increased in 1975, but this would scarcely lead to a reduction in efficacy of the vaccine.

There has, however, been increased use of jet injection since 1973, and perhaps also an increase in vaccination by multiple puncture techniques. The extent of these changes

is also not known, but may well be substantial. Jet injection instruments show considerable technical variations (British Thoracic and Tuberculosis Association 1971*a*) and may be used by inadequately trained personnel. Multiple-puncture techniques do not give such satisfactory post-vaccination tuberculin sensitivity as do syringe and needle (British Thoracic and Tuberculosis Association 1971*b*). If a proportion of those classified as vaccinated have remained unprotected due to inadequacies of vaccination technique this could have obscured the effect of a decline in infection risk between 1973 and 1978.

Comparison with results of controlled trial started in 1950–52

The results presented have shown that the effectiveness of the schools BCG vaccination scheme in preventing notifications of tuberculosis in the calendar years 1973 and 1978 is between 69% and 88%. These results are very similar to those obtained in the Medical Research Council's controlled trial of BCG vaccination of slightly older school children in 1950–52. The protective effectiveness in that trial was 77% over a 20-year period, though little or no effect was shown in the last five years (Hart & Sutherland 1977).

The similarity of the protective effectiveness in that controlled trial and in routine use in the present study is of interest especially because of the considerable differences recorded in tuberculosis rates. In the first five years of the trial the rates in the tuberculin-negative and BCG-vaccinated groups were 250 and 40 per 100 000 respectively, and these may reasonably be compared with the rates of 10.5 and 2.6 per 100 000 in the 15–19 age group for life-time residents of England and Wales in 1978 shown in the present study. In the second five years of the Medical Research Council trial the rates in these groups were 106 and 33 per 100 000, compared with 17.4 and 4.2 per 100 000 in the 20–24 age group in the present study.

Even in the tuberculin-positive group the rates have fallen considerably, from 149 per 100 000 in the first five years of the Medical Research Council trial to 14.1 per 100 000 at age 15–19 in 1978, and from 53 per 100 000 in the second five years of the trial to 7.6 per 100 000 at age 20–24 years in 1978.

Number of notifications prevented by BCG vaccination

This is an alternative method of expressing the results which was used in the report of the 1973 study (British Thoracic and Tuberculosis Association 1975). The estimates given below differ from those given in that report for two reasons:

1. The change in method in estimating the populations at risk, the details of which are recorded earlier in this paper. The method now adopted is regarded as giving more reliable estimates.

2. The more complete data now available for the cohort aged 15–19 years in 1973 has led to a revision of the estimates for that as well as the subsequent cohort.

The first line of Table VII shows the number of notifications that would have been prevented in 15 years following 100 000 vaccinations in 1950–52. In the first five years of that study the annual notification rate was 210 per 100 000 less in BCG vaccinated subjects than in tuberculin-negatives, in the second five years it was 73 per 100 000 less, and in the third five years it was 16 per 100 000 less, with little difference subsequently. Each of these rates was considered to operate for a five-year period, so that the total reduction in notifications from 100 000 vaccinations at that time would have been

Retrospective studies

Give a rough assessment -
in situations where case finding/detection + notification is good -

5 (210 + 73 + 16) = 1495. This can also be expressed in the form that 67 vaccinations at that time would have prevented one notification in the next 15 years.

The results from the present report are expressed in similar form in the lower part of Table VII, but some additional assumptions are made. For the cohort vaccinated in 1967–71 reasonably direct measurements of the notifications prevented are available for 1973 and 1978, representing the notifications prevented at ages 15–19 and 20–24 years. At age 15–19 years the reduction is 21.1 – 2.5 = 18.6 per 100 000 per year falling to 17.4 – 4.2 = 13.2 per 100 000 at age 20–24 years in 1978. It is then assumed that the fall in notifications prevented between age 20–24 years and age 25–29 years is in the same proportion as between age 15–19 years and age 20–24 years. This gives 5(18.6 + 13.2 + 9.4) = 206 notifications prevented in 15 years following 100 000 vaccinations in 1967–71.

Table VII. Estimates of notifications prevented in 15 years following 100 000 vaccinations in England and Wales

Period of vaccination	*Notifications prevented*	*Vaccinations to prevent one notification*
1950–52 (MRC)	1495	67
1967–71	206	500
1972–6	88	1150
1977–81	44	2300
1982–6	22	4600

For the next cohort only the reduction in notifications at age 15–19 years in 1978 is directly available (7.9). It is assumed that the reduction in the two older five-year age groups are in the same proportion as for the preceding cohort, to give a figure of 5(7.9 + 5.6 + 4.0) = 88 notifications prevented in 15 years after 100 000 vaccinations in 1971–6. The remaining two lines of Table VII are based on the assumption that the infection risk and number of cases prevented continue to fall by about 50% in five years and lead to a figure of 44 cases prevented in 15 years by each 100 000 vaccinations in the period 1977–81.

ACKNOWLEDGEMENTS

The Research Committee is most grateful to the many chest physicians, medical officers of environmental health and specialists in community medicine (child health), too numerous to list by name, who supplied the information on which the survey depended. Special tabulations were made available by the Office of Population Census and Surveys, the Scottish Home and Health Department and the Department of Health and Social Security, who also provided financial support.

Reprints can be obtained from the Administrative Secretary, British Thoracic Association, 30 Britten Street, London SW3 6NN.

References

British Thoracic and Tuberculosis Association (1971*a*) A comparison of intradermal BCG vaccination by jet injection and by syringe and needle. *Tubercle 52*, 155.

British Thoracic and Tuberculosis Association (1971*b*) BCG vaccination by multiple puncture: Fourth Report. *Tubercle 52*, 19.

British Thoracic and Tuberculosis Association (1973) A tuberculosis survey in England and Wales 1971; the influence of immigration and country of birth upon notifications. *Tubercle 54*, 249.

British Thoracic and Tuberculosis Association (1975) Present effectiveness of BCG vaccination in England and Wales. *Tubercle 56*, 129.

British Thoracic Association (1978) A study of a standardised contact procedure in tuberculosis. *Tubercle 59*, 245.

Census, Great Britain (1971) Country of Birth Tables unpublished extension of Table 2 (for residents in England and Wales) (Table DT 14). London: HMSO.

Christie, P. N. & Sutherland, I. (1976) A national tuberculin survey in Great Britain 1971–73. *Bull. Un. int. Tuberc. 51*, 185.

Hart, P. D'A. & Sutherland, I. (1977) BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. Final Report to the Medical Research Council. *Br. med. J. 2*, 293.

Lunn, J. A. & Johnson, A. J. (1978) Comparison of the tine and Mantoux tuberculin tests. Report of the Tuberculin Subcommittee of the Research Committee of the British Thoracic Association. *Br. med. J. 1*, 1451.

Office of Population Censuses and Surveys (1975) *The Registrar General's Revised Estimates of the Population of England and Wales, Regions and Local Authority Areas 1961 to 1971*. London: HMSO.

Office of Population Censuses and Surveys (1977) *New Population Estimates for England and Wales, mid-1971 to mid-1976*. OPCS Monitor PP1 77 3. London: HMSO.

Office of Population Censuses and Surveys (1979) *Revised Population Estimates for the United Kingdom and Great Britain, mid-1971 to mid-1977*. OPCS Monitor PP1 79 4. London: HMSO.

Springett, V. H. (1976) Do we need BCG vaccination? *Postgrad. med. J. 52*, 584.

Stilwell, J. A. (1976) The benefits and costs of the schools BCG vaccination programme. *Br. med J. 1*, 1002.

The BCG Controversy

A Methodological and Statistical Reappraisal

John D. Clemens, MD; Jackie J. H. Chuong, MD; Alvan R. Feinstein, MD

• **Because of the conflicting results of eight major controlled trials, BCG vaccination against tuberculosis remains controversial despite more than 50 years of use. Suspecting a methodological source for the controversy, we reviewed the scientific and statistical quality of each trial. The analysis showed that (1) although biased allocation of the vaccine appeared an unlikely explanation for the disparate results, adequate demonstration of unbiased detection of tuberculosis was available only for the three trials reporting 75% or greater protective efficacy; and (2) in most trials reporting low efficacy, the results had wide confidence intervals that could not exclude high efficacy, but the trials reporting high efficacy all had narrow confidence intervals that excluded low efficacy. Because the trials with the best methodological quality and greatest statistical precision reported high efficacy, the evidence suggests that BCG can confer a high degree of protection against tuberculosis and that bias or inadequate statistical power may have contributed to the conflicting data.**

(*JAMA* 1983;249:2362-2369)

BCG VACCINE remains a highly controversial method of preventing tuberculosis despite more than 50 years of use and its current status as a compulsory or an officially recommended vaccine in 182 countries and territories.[1] During its early years, BCG was alleged to be toxic, mainly because 72 German children died in 1930 after receiving vaccine contaminated by virulent non-BCG mycobacteria.[2] After exoneration for this episode, BCG was accepted as safe, but doubts were raised about its efficacy. Although numerous studies were conducted to evaluate BCG, only eight large-scale community trials[3-28] evaluated BCG efficacy against tuberculosis morbidity in an acceptably controlled fashion.[29-34] These trials reported conflicting results, leading to the current controversy.

For editorial comment see p 2376.

From the Departments of Medicine (Drs Clemens, Chuong, and Feinstein) and Epidemiology (Dr Feinstein) and The Robert Wood Johnson Clinical Scholars Program (Drs Clemens and Feinstein), Yale University School of Medicine, New Haven, Conn; and the Cooperative Studies Program Support Center, Veterans Administration Hospital, West Haven (Dr Feinstein)

Reprint requests to 333 Cedar St, New Haven, CT 06510 (Dr Clemens)

Table 1 shows the basic features and inconsistent results of the eight trials, which are arranged chronologically according to their dates of inception. Vaccine accomplishment is cited as "protective efficacy," a standard index devised by Greenwood[35] and his colleague Yule to indicate the proportion of disease reduction that is attributable to vaccine. The index is calculated as follows: {[(tuberculosis attack rate in controls)−(tuberculosis attack rate in vaccinees)]/(tuberculosis attack rate in controls)}×100%. This table displays the final values reported by each trial for BCG protective efficacy against tuberculosis incidence. The wide range of BCG protective efficacy values reported by the trials extended from 80%, reflecting substantial protection by the vaccine, to −56%, indicating a higher rate of tuberculosis among vaccinees than controls.

With the general assumption that the trials contained no serious methodological flaws, the disparities in results have usually been attributed to different biologic conditions in the individual studies.[29-33,36] The most commonly cited biologic sources of intertrial variation have been differences in nutritional status,[31] in the prevalence and virulence of *Mycobacterium tuberculosis*,[31,36] in the prevalence of atypical mycobacteria,[31] and in the potency of BCG.[30,32] Although several of these hypotheses are theoretically attractive, none has provided an entirely convincing explanation for the controversy.[34]

Because the current controversy is based on the inadequately explained disparities in results of these eight trials, and because the methodological quality of the trials has not been thoroughly evaluated, we examined the published reports of the trials to appraise their methodological and statistical features. In instances where the published reports include too few details to permit assessment,

Table 1.—Results of Eight Major Controlled Trials of BCG Immunization Against Tuberculosis

North American Indians[54]	1935	Children and young adults	9-11	3,006	80
Georgia[45-47]	1947	Children	20	4,839	−56
Georgia-Alabama[48,49,51]	1950	General population	20	34,787	6
Madanapalle[52,53]	1950	General population	16-21	10,877	20

*Denotes longest follow-up for which BCG protection against tuberculosis morbidity was assessed.

†Refers to efficacy of BCG, not vole-bacillus vaccine.

‡Actual observed protective efficacy was not calculable, since exact numbers of subjects receiving and not receiving vaccine were not listed. The −32% protective efficacy assumes that the allocation scheme vaccinated the intended proportion (two thirds) of subjects.

authors of the reports were contacted directly to answer specific questions that pertained only to the missing information. To preserve comparability of the trials in the evaluation, we considered only reports detailing the efficacy of BCG in reducing the occurrence of clinical tuberculosis. We thus excluded from consideration one report[1] that evaluated only the efficacy of BCG in reducing tuberculosis mortality.

METHODOLOGICAL EVALUATION

In the basic design of the BCG trials, subjects free of clinical tuberculosis and otherwise eligible for the trials were allocated to BCG vaccine or control groups. At the time of allocation, each subject could be described according to several baseline demographic and clinical features—apart from vaccination status—that might influence future susceptibility to tuberculosis. After allocation, the subjects were followed up with varying mechanisms of observation and for various periods of time to detect the occurrence or nonoccurrence of tuberculosis.

Since different people can have different degrees of prevaccination susceptibility to tuberculosis, and since the subsequent identification of tuberculosis requires special diagnostic procedures, eg, chest roentgenograms and microbiologic examinations, four types of precaution are necessary to avoid bias in a long-term comparison of the prophylactic efficacy of BCG *v* no BCG: (1) When the subjects are allocated to receive or not receive BCG, they should be similarly distributed with respect to their susceptibility to tuberculosis. (2) When the two groups are followed up thereafter, they should receive equal surveillance in follow-up examinations to discern any symptoms or other phenomena that would evoke the ordering of diagnostic tests. (3) When such tests are ordered, they should be solicited equally in both groups. (4) When the evidence of the tests and other data are interpreted, the interpretations should be performed without knowledge of the patient's vaccination status.

The biases that can arise if these precautions are not maintained are called (1) *susceptibility bias*, (2) *surveillance bias*, (3) *diagnostic-testing bias*, and (4) *diagnostic-interpretation bias*.

In modern clinical trials of therapy, specific standards have been developed to safeguard against these biases.[55] Thus, formally randomized and double-blinded allocation of therapy can be used to protect against susceptibility bias, and the distributions of pertinent baseline characteristics can be analyzed to assure the absence of susceptibility bias. Comprehensive and demonstrably equal follow-up of the compared groups offers protection against surveillance bias. Frequently scheduled diagnostic tests, obtained in all members of the compared groups, help safeguard against diagnostic-testing bias, particularly when double-blinding is used to ensure equal requesting of tests. Finally, the use of uniform diagnostic criteria that are "blindly" applied to the diagnostic data for each member of the study population protects against diagnostic-interpretation bias.

Unfortunately, none of the BCG trials was conducted with all of these modern standards, probably because of several factors that may have precluded an ideal experimental design. Most of the studies were initiated before widespread appreciation of modern standards for clinical trials. In addition, the low incidence of tuberculosis in the study populations required that large study groups be followed for long intervals, creating formidable logistic barriers to complete follow-up and frequently scheduled diagnostic tests. Furthermore, other problems in conducting trials in "underdeveloped" regions undoubtedly imposed additional constraints. Finally, the cutaneous scars left by BCG and the ethical problems of creating comparable placebo scars prevented the use of double-blind methods for masking the vaccination status of each participant.

If every trial that is not ideal is to be eliminated from consideration, however, the rejection would prevent the future possibility of evaluating BCG and would also eliminate the current possibility of forming judgments from available evidence. Although none of the trials was perfect, we considered it important to evaluate the substantial degree of variation in methodological quality that can exist among trials that are not ideal. We therefore decided to evaluate the performance of the trials according to uniform criteria, established before the review, that represented the minimum safeguards necessary to provide reasonable assurance of valid results, even when the ideal safeguards were not applied. Because many details of the methods were published in sections devoted to presentation or discussion of results,

the trials could not be evaluated without an awareness of their conclusions. This problem did not seem cogent in the current analysis, however, since the review was performed without any preconceived hypotheses about what might be found. In addition, the criteria used for the evaluation involved little or no subjective judgment, and total agreement was found[3] in ratings given by two independent assessors of the trials (J.D.C. and J.J.H.C.).

The explicit criteria for the evaluation, together with detailed reasons for negative ratings, are given in the sections that follow.

Table 2.—Protection Against Susceptibility Bias in Eight Major Controlled Trials of BCG Immunization Against Tuberculosis*

	Satisfactory Allocation Safeguards?	Equal Distribution of Tuberculosis Risk?
North American Indians	Yes	Yes
Chicago	No†	No
Georgia	Yes	Yes
Puerto Rico	Yes	Yes
Georgia-Alabama	Yes	Yes
England	Yes	Yes
Madanapalle	No‡	Yes
Chingleput	Yes	No§

*See text for explanation.

†Haphazard BCG assignment scheme.

‡Vaccinators had control over BCG assignment. No placebo was used, and number of postallocation vaccine refusers was substantial (14% of those assigned to BCG).

§Distribution of susceptibility factors was not examined.

Protection Against Susceptibility Bias

For unbiased allocation of baseline susceptibility characteristics, the assignment of therapy should be executed by a mechanism that is independent of investigator and subject preference. Since only one trial (Chingleput) used formally random and double-blinded allocation, we tried to identify alternative tactics that might provide reasonable protection against susceptibility bias. Accordingly, in the other seven trials, we judged the vaccine allocation mechanism to be satisfactory if it exhibited all of the following characteristics: (1) Eligibility for inclusion in the trial was determined before the vaccine was assigned. (2) BCG was assigned by a systematic rather than haphazard mechanism. The mechanism should preferably have depended on a characteristic (eg, registration number) unrelated to tuberculosis susceptibility. If a characteristic potentially related to tuberculosis risk (eg, birth year) was used for this purpose, the assignment mechanism should have attempted to balance the distribution of this characteristic in the BCG and control groups. For example, the age distribution among vaccinees and controls could be balanced by vaccinating according to even and odd birth years. (3) BCG was assigned without personal familiarity with the subjects. To achieve this objective, the particular people who acted as vaccinators should not have been responsible for making decisions about which subjects were to be vaccinated. (4) A placebo injection was used, or records showed that relatively few subjects (eg, <5% of those allocated to the vaccine) refused vaccination, or there was evidence that the number of tuberculosis cases among the refusals was too small to have altered the results, even if the refusals had been counted as "vaccinees." Vaccine refusals should not have been included among the controls.

In addition to the problem of vaccine refusals, each trial was potentially susceptible to certain additional types of "irregularities," ie, events that violate the intent of the four allocation safeguards. Examples include erroneous administration of the vaccine and exclusions performed with knowledge of vaccine assignment. If such irregularities were demonstrably trivial, it would be unfair to downgrade a trial as violating the allocation safeguards. Furthermore, since the analysis of such irregularities remains controversial, even in the modern clinical trial literature,[40] it would be excessive to demand that the authors analyze the irregularities in any one particular fashion. To accommodate these considerations, we gave credit for adequate safeguards if the only violations consisted of a small number of irregularities (eg, <5% of the study population), or if the total occurrence of tuberculosis in the irregular group was insufficient to alter the trial results.

Beyond these safeguards in the allocation of vaccine, the data should have been checked to show an equitable distribution of several well-recognized tuberculosis susceptibility factors in the vaccine and control groups. Examples of these susceptibility factors include age, gender, and history of exposure to tuberculosis.[41]

Table 2 rates each trial according to the adequacy of allocation safeguards and the equality of the distributions for susceptibility factors. Reasons for negative ratings are given in the footnotes. If a trial used double-blinded and randomized allocation, or if it fulfilled all four of the salient criteria for unbiased allocation, credit was given for satisfactory allocation safeguards. If any of the allocation criteria were not fulfilled, credit was not given. Tuberculosis risk was considered equally distributed if all examined susceptibility factors occurred with equal frequency among vaccinees and controls, or if subsequent analysis (eg, stratification) showed that unequally distributed factors had had no consequential effect on protective efficacy. Credit was not given for equal susceptibility distribution if the distribution was not reported, or if any factors were distributed in an unequal way that might have substantially altered the trial results.

All but the Chicago and Madanapalle trials provided acceptable evidence against biased allocation. The Chicago trial lacked a systematic method of vaccine allocation, using instead an ad hoc scheme that balanced the numbers of vaccinees and controls within clusters of subjects. However, because this assignment was performed without personal familiarity with subjects, and since all other safeguards were fulfilled, it seems unlikely that this ad hoc allo-

cation scheme could have created significant susceptibility bias. In the Madanapalle trial, a substantial fraction (14%) of eligible subjects admitted to the trial refused the vaccine after allocation, and the BCG assignments were made by the vaccinators. The impact of the former violation was probably negligible, since protective efficacy would be unaffected by the retention of refusals in the vaccine group, even if the control incidence rates of tuberculosis are postulated for the refusers. The importance of the latter violation is difficult to ascertain.

When the distribution of age, gender, and other tuberculosis susceptibility factors was examined among the vaccinees and controls in seven trials, the few instances of unequal distributions were found to be of trivial importance, since they did not substantially alter the observed protective efficacy. Since the distribution of tuberculosis susceptibility factors among vaccinees and controls was not examined in the eighth trial (Chingleput), it did not receive credit for the safeguard. Since, however, the Chingleput trial used double-blinded and formally randomized vaccine allocation and employed an extremely large sample size, susceptibility bias is an unlikely explanation for the observed result.

Protection Against Surveillance Bias

We considered surveillance bias to be unlikely if the investigators used a schedule of follow-up procedures that maintained contact with equal and extensive (≥70%) proportions of the BCG and control groups. Because the level of follow-up in most trials varied with the length of time after vaccine administration, credit was given if equal and extensive follow-up was documented and if the final assessment of BCG efficacy was not altered by cases detected after the last point in time at which follow-up was equal and extensive. The first main column in Table 3 shows the rating of each trial according to its compliance or noncompliance with these criteria. Reasons for negative ratings are cited in the footnotes. Only the North American Indian, England, and Chicago trials provided adequate evidence that surveillance bias was unlikely.

Table 3.—Protection Against Biased Detection of Tuberculosis in Eight Major Controlled Trials of BCG Immunization Against Tuberculosis*

Trial	Adequate Protection Against		
	Surveillance Bias?	Diagnostic-Testing Bias?	Diagnostic-Interpretation Bias?
North American Indians	Yes	Yes	Yes
Chicago	Yes	Yes	Yes
Georgia	No†	No‡	No§
Puerto Rico	No†	No‡	No§
Georgia-Alabama	No†	No‡	Equivocal‖
England	Yes	Yes	Yes
Madanapalle	No¶	No#	Probable**
Chingleput	No††	No‡‡	Yes

*See text for explanation.

†No scheduled follow-up procedures.

‡Frequencies and indications for chest roentgenograms were not reported.

§No diagnostic review.

‖Incomplete diagnostic review was performed in blinded fashion for one early progress report; subsequent reports added cases diagnosed without blinded reviews and having a potentially substantial impact on final results.

¶Study population was actively followed up, but level of follow-up was inadequate to exclude surveillance bias.

#Chest roentgenogram frequencies were equal for early surveys but unknown for final survey, which had potentially important impact on final results. Protective efficacy was not shown to be unaffected by tuberculosis cases detected during routine care.

**Complete diagnostic reviews were performed in blinded fashion for all progress reports; final report added cases diagnosed without blinding but with modest potential impact on final results.

††Study population actively followed up, but level of follow-up unclear in tuberculin-negative vaccinees and controls.

‡‡Protective efficacy was not shown to be unaffected by tuberculosis cases detected during routine care, and there was inadequate proof of equal chest roentgenogram frequencies during all mass roentgenographic surveys.

Protection Against Diagnostic-Testing Bias

Because BCG frequently leaves a conspicuous scar or pigmentary alteration, it was impossible to conduct the trials in a double-blinded fashion. In lieu of double-blinding, it was crucial that each trial provide documentation that biased detection of tuberculosis did not occur as a result of unequal intensity of diagnostic testing in the BCG and control groups. Since chest roentgenograms were the basic case-finding tests for all of the trials and were the confirmatory tests for some of the trials, we considered diagnostic-testing bias to be improbable if chest roentgenograms were applied in a demonstrably equal fashion in the vaccine and control groups.

To assess whether chest roentgenograms were applied with equal frequencies and for the same indications in vaccinees and controls, it was necessary to contemplate the two basic settings in which the films were obtained. In the first setting, chest roentgenograms were imposed on subjects either in mass population surveys or in scheduled follow-up appointments. With these types of systematic roentgenographic follow-up, x-ray films were obtained irrespective of clinical indications, and the identified tuberculosis cases would not bias BCG efficacy if the surveys covered equal numbers of vaccinees and controls and if the roentgenograms were read "blindly." In the second setting, chest roentgenograms were obtained to evaluate patients because of symptoms during routine clinical care. This use of chest roentgenograms might easily have biased BCG efficacy, since the likelihood of obtaining an x-ray film depended on both a subject's motivation to seek medical care and a physician's diagnostic suspicion and since neither the physician nor the subject was "blinded" to BCG status.

Based on these considerations, we regarded diagnostic testing bias as unlikely in trials with systematic roentgenographic follow-up if the frequency of "blindly" read chest x-ray films obtained in a scheduled fashion was similar for vaccinees and controls, and if the reported overall level of BCG efficacy was unaffected by the inclusion of additional cases detected during routine clinical care. As shown in the second main column of Table 3,

three of the five trials using systematic chest roentgenographic follow-up—North American Indians, Chicago, and England—fulfilled these criteria. It should be noted here that one of these trials (England) used serial mass roentgenographic surveys only for the first nine years of follow-up, relying on routine diagnoses for the remaining 11 years of the study. Relatively few cases, however, were detected during the last half of the follow-up period (37 of the total 336 cases in originally tuberculin-negative subjects), and the inclusion of cases detected during routine clinical care did not alter the overall assessment of BCG efficacy. Moreover, protective efficacy was demonstrated to be similar for cases detected during mass roentgenographic screening and cases detected during routine care. Therefore, credit was given for adequate protection against diagnostic testing bias.

For trials relying exclusively on ad hoc routine clinical care to identify tuberculosis cases, convincing evidence against diagnostic testing bias required documentation that chest roentgenograms were obtained with equal frequencies and for similar indications in the vaccine and control groups. As indicated in Table 3, none of these three trials—Georgia, Georgia-Alabama, and Puerto Rico—collected data that were necessary to document indication-specific equality of chest roentgenograms, or even data about the overall frequencies of chest x-ray films or other diagnostic tests for tuberculosis in the compared groups.

Protection Against Diagnostic-Interpretation Bias

We regarded diagnostic-interpretation bias as unlikely if the pertinent clinical data on all tuberculosis cases and suspects were reviewed in a manner blinded to vaccination status. The third column of Table 3 shows that these criteria were unequivocally fulfilled only by the North American Indian, Chicago, England, and Chingleput trials. Ratings of two of the remaining trials require special explanation. In its final report,[28] the Madanapalle trial relied exclusively on microscopic or cultural evidence, interpreted without blinding, for diagnosis of tuberculosis. That this procedure might have posed a problem is suggested by comparison with a previous report,[29] in which a blinded review of roentgenographic evidence rejected the diagnoses of tuberculosis in approximately 14% of the laboratory isolates. Nevertheless, since results for BCG efficacy obtained by either method were approximately the same, and since inclusion of unblinded laboratory diagnoses resulted in a value for BCG protective efficacy that was only 13% below the level based on previous blinded diagnoses, this trial was given a rating of "probable." An early report on the Georgia-Alabama trial[11] described the unbiased nature of the trial results, based on a blinded review of a portion of the evidence (roentgenograms) used in the study's criteria for tuberculosis. Results of the review, however, were neither cited nor directly used for final tuberculosis diagnosis. No further reviews were performed, and subsequent diagnoses, which constituted the majority of diagnoses in the study, reduced BCG protective efficacy by 30%. Because the results of the study were dominated by unblinded diagnoses that were not demonstrated to be unbiased, the trial was scored "equivocal."

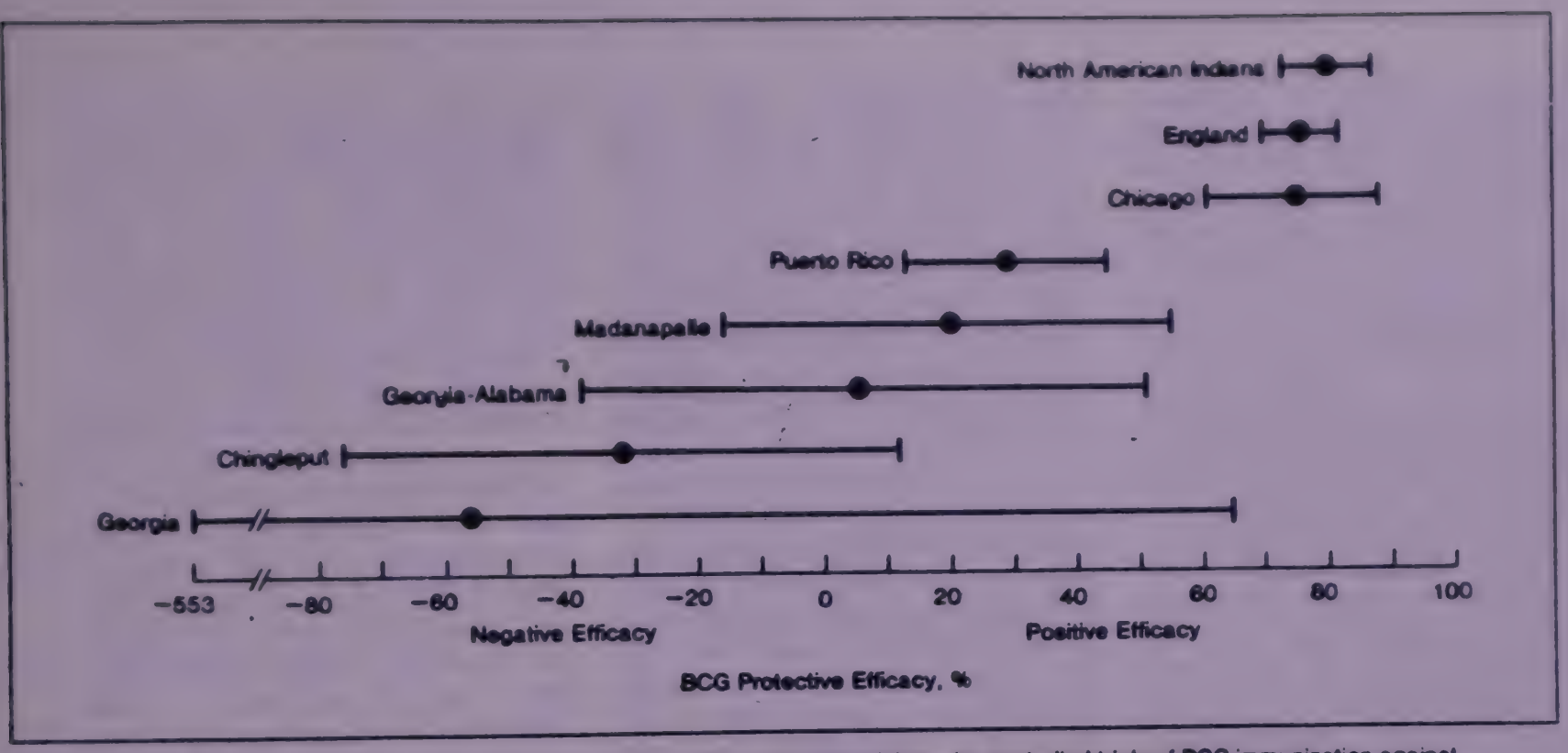
Statistical Considerations

In addition to these methodological distinctions, each trial can be appraised according to the statistical precision of its result. In assessing statistical precision, one answers the question, "Given the level of protective efficacy observed in the trial, what range of protective efficacy values might have arisen by chance alone?" To estimate this range for all trials apart from the Georgia trial, 95% confidence intervals were calculated, using the normal approximation formula appropriate for ratios of random variables.[27] Because of the small number of cases in the Georgia trial, the method of Walter[30] was used to calculate the 95% confidence interval for this trial. The Figure denotes each trial's observed value for BCG protective efficacy by a point and displays the 95% confidence interval as a bar on either side of the observed result. The narrower the confidence interval, the more precise is the estimate of BCG's protective efficacy.

Although each trial reporting very high (≥75%) protective efficacy had precise results that excluded low protective efficacy, the lower values for protective efficacy reported by the remaining five trials had considerably poorer precision. Four of these five trials had confidence intervals that could not exclude substantial (≥45%) protective efficacy, and two of these five trials had intervals in which upper boundaries either overlapped or almost overlapped the confidence intervals for the high efficacy trials. Thus, although trials reporting high protective efficacy values had narrow confidence intervals that confirmed the precision of the results, several of the trials reporting low efficacy values lacked statistical precision and could not exclude substantial BCG efficacy.

Summary of the Ratings

Table 4 ranks the trials in order of decreasing observed protective efficacy values and summarizes the ratings given to each trial for the quality of protection against potential biases and for the adequacy of statistical precision. In this table, trials scored in Table 2 as adequate for allocation safeguards and for demonstrably equal tuberculosis risk received credit for adequate protection against susceptibility bias; trials whose violations of allocation safeguards were regarded as inconsequential were rated as "probable"; and the trial in which the impact of safeguard violation could not be ascertained as trivial was scored as "equivocal." Ratings for protection against surveillance, diagnostic-testing, and diagnostic-interpretation biases are identical to those given in Table 3. Statistical precision was assessed from the Figure. The three trials reporting high BCG efficacy (North American Indian, England, and Chicago) were rated as having adequate precision, since the lower boundaries of their confidence intervals for protective efficacy remained at high levels (≥61%). Among the five trials reporting low efficacy, all but the Chingleput trial were scored as having inadequate precision, since the upper boundaries of their confidence intervals did not exclude substantial BCG efficacy (≥45%). Table 4 shows a strikingly direct relationship between trials reporting high BCG efficacy and the



Ninety-five percent confidence intervals for protective efficacy found in eight major controlled trials of BCG immunization against tuberculosis. Each trial is identified to left of its corresponding confidence interval. Within each confidence interval, solid circle denotes reported value of protective efficacy.

Table 4.—Protection Against Bias and Adequacy of Statistical Precision in Eight Major BCG Trials*

Trial	Adequate Protection Against: Susceptibility Bias?	Surveillance Bias?	Diagnostic-Testing Bias?	Diagnostic-Interpretation Bias?	Adequate Statistical Precision?	Observed Protective Efficacy, %
North American Indians	Yes	Yes	Yes	Yes	Yes	80
England	Yes	Yes	Yes	Yes	Yes	76
Chicago	Probable	Yes	Yes	Yes	Yes	75
Puerto Rico	Yes	No	No	No	No	29
Madanapalle	Equivocal	No	No	Probable	No	20
Georgia-Alabama	Yes	No	No	Equivocal	No	6
Chingleput	Probable	No	No	Yes	Yes	−32
Georgia	Yes	No	No	No	No	−56

*See text for explanation.

associated safeguards against bias and adequacy of statistical precision.

COMMENT

Although the results of this analysis do not exclude the role of biologic disparities in the conflicting results of BCG trials, the analysis indicates that the eight trials varied considerably in their methodological protection against bias and in their statistical capacities. Furthermore, amid this methodological and statistical heterogeneity, trials demonstrating higher protective efficacy were generally superior to trials demonstrating lower protective efficacy. Although our analysis does not allow conclusions about the most likely "true" level of BCG protective efficacy, it is nevertheless striking that only the North American Indian and England trials—both of which reported protective efficacy of 76% or more—rated highly in all of the examined aspects of methodological and statistical quality.

Leniency of Criteria

Several issues may be raised by our method of analysis. First, it might be argued that our criteria for assessment were excessively lenient. Indeed, if evaluated by more ideal standards, such as those proposed by Gifford and Feinstein[9] for trials of anticoagulant therapy for myocardial infarction, the data published from all eight BCG trials might be regarded as scientifically inadmissible evidence. Nevertheless, imperfect data must often be used for important policy decisions, such as the recommendations for future BCG immunization recently published by a World Health Organization study group.[1] To set realistic standards that preserve the ideal goals, while allowing for inevitable methodological compromises engendered by the formidable logistic obstacles in the BCG trials, we decided to establish the salient criteria used in this review.

Correlation of Methods and Results

Second, no explanation has yet been offered for the finding of high efficacy values in the trials that had a better methodological "process." No important differences in the quality

of allocation safeguards could be found between trials reporting high efficacy and trials reporting low efficacy. In addition, the populations under study had no evidence of past tuberculosis infection and were relatively homogeneous in their low inherent risk for acquiring tuberculosis. Susceptibility bias, therefore, cannot be offered as an explanation for the conflicting results.

The main source of vulnerability in the eight trials seems to have been "detection bias." The assessment of BCG efficacy rested on only a small number of tuberculosis cases, but double-blind methods could not be used to detect and diagnose those cases. Furthermore, two of the trials have published data demonstrating a substantial frequency of tuberculosis that is not detected by routine clinical care. The England trial reported that more than half of the tuberculosis cases detected in the trial emerged from mass roentgenographic screening, rather than from the clinical care of symptomatic patients." Similarly, in Muscogee County, Georgia (site of the Georgia and Georgia-Alabama trials), a single survey covering a portion of a population cohort in early 1950 detected 25% of all known incident cases developing in the cohort between 1947 and 1951.[4] The reservoir of tuberculosis that is not detected during routine clinical care constitutes the "substrate" on which detection bias may operate. For example, if the conditions of vaccinated subjects were more intensively evaluated with diagnostic tests for tuberculosis because of the tuberculin positivity produced by the vaccine or because of a special interest in identifying cases in subjects with BCG scars, cases of tuberculosis that might otherwise have escaped detection during routine clinical care would selectively be detected in the BCG group, resulting in diminished vaccine protective efficacy. Trials that lacked such tactics as systematic roentgenographic follow-up to protect against detection bias were therefore susceptible to potentially substantial distortions by this bias.

Another way that detection bias could have operated was in the diagnosis of tuberculosis once the diagnostic data had been acquired. Among the five trials reporting protective efficacy values of 29% or less, the Puerto Rico, Georgia, and Georgia-Alabama investigators either accepted routine diagnoses of tuberculosis made with the knowledge of tuberculin status, or actually used tuberculin positivity as a criterion for tuberculosis in the course of a diagnostic review. Since BCG, per se, induces tuberculin positivity in a substantial proportion of vaccinees, these three trials could have overestimated the incidence of tuberculosis in vaccinees, thereby underestimating BCG protective efficacy.

Problems in Evaluating Details

Third, because we were equally critical of overt methodological flaws and of data insufficient to allow methodological assessment, it might be argued that we were unfair in giving low ratings to reports that did not include adequate details. For this reason, we personally contacted authors from each trial. Thus, none of the low ratings arose because of inadequate consideration of currently available information. Since, however, the recent Chingleput trial has not yet undertaken analyses necessary to confirm the efficacy of its methodological safeguards, and since our appraisals are based on the inadequacy of documentation, final appraisal of the methodological quality of this trial will have to await its future reports.

Finally, two points deserve emphasis. First, although the better ratings for methodological and statistical quality given to trials reporting high BCG efficacy suggest that their results are valid, the lower ratings given to trials reporting low BCG efficacy do not refute the negative results, but merely indicate that methodological variation may have contributed to the results. Second, our analysis is concerned only with the intrinsic efficacy of BCG in preventing tuberculosis. Importantly, the decision to use BCG in a particular epidemiologic situation requires examination of additional factors beyond intrinsic efficacy. To formulate a rational policy for BCG, consideration must be given to the incidence of tuberculosis that is potentially preventable by BCG, the costs of implementing widespread BCG vaccination, and the costs and effectiveness of alternative forms of tuberculosis control.[45]

The following authors provided additional details for our analysis: George Comstock (Georgia, Georgia-Alabama, and Puerto Rico trials); Johannes Frimodt-Møller (Madanapalle trial); Sol Rosenthal (Chicago trial); Lawrence Shaw (North American Indian trial); Ian Sutherland (England trial); and S. W. Tripathy (Chingleput trial). Stephen D. Walter provided statistical advice.

References

1. BCG vaccination policies, report of WHO study group. *WHO Tech Rep Ser*. 1980, pp 1-17.
2. Guérin C: The history of BCG, in Rosenthal S (ed): *BCG Vaccination Against Tuberculosis*. Boston, Little Brown & Co, 1957, pp 48-53.
3. Townsend J, Aronson J, Saylor R, et al: Tuberculosis control among North American Indians. *Am Rev Tuberc* 1942;45:41-52.
4. Aronson J, Palmer C: Experience with BCG vaccine in the control of tuberculosis among North American Indians. *Public Health Rep* 1946;61:802-820.
5. Aronson J: Protective vaccination against tuberculosis with special reference to BCG vaccination. *Am Rev Tuberc* 1948;58:255-281.
6. Aronson J, Aronson C: Appraisal of protective value of BCG vaccine. *JAMA* 1952;149:334-343.
7. Stein S, Aronson J: The occurrence of pulmonary lesions in BCG vaccinated and unvaccinated persons. *Am Rev Tuberc* 1953;68:695-712.
8. Aronson J, Aronson C, Taylor H: A 20-year appraisal of BCG vaccination in the control of tuberculosis. *Arch Intern Med* 1958;101:881-893.
9. Rosenthal S, Loewinsohn E, Graham M, et al: BCG vaccination against tuberculosis in Chicago. *Pediatrics* 1961;28:622-641.
10. Shaw L: Field studies on immunization against tuberculosis: I. Tuberculin allergy following BCG vaccination of school children in Muscogee County, Georgia. *Public Health Rep* 1951;66:1415-1426.
11. Comstock G, Shaw L: Controlled trial of BCG vaccination in a school population. *Public Health Rep* 1960;75:583-594.
12. Comstock G, Webster R: Tuberculosis studies in Muscogee County, Georgia: VII. A 20 year evaluation of BCG vaccination in a school population. *Am Rev Respir Dis* 1969;100:839-845.
13. Palmer C, Shaw L, Comstock G: Community trials of BCG vaccination. *Am Rev Respir Dis* 1958;77:877-907.
14. Comstock G, Edwards P: An American view of BCG vaccination, illustrated by results of a controlled trial in Puerto Rico. *Scand J Respir Dis* 1972;53:207-217.
15. Comstock G, Livesay V, Woolpert S: Evaluation of BCG vaccination among Puerto Rican children. *Am J Public Health* 1974;64:289-291.
16. Comstock G, Palmer C: Long-term results of BCG vaccination in the southern United States. *Am Rev Respir Dis* 1966;93:171-183.
17. Comstock G, Woolpert S, Livesay V: Tuberculosis studies in Muscogee County, Georgia: Twenty-year evaluation of a community trial of BCG vaccination. *Public Health Rep* 1976;91:276-280.
18. Great Britain Medical Research Council: BCG and vole bacillus vaccines in the prevention

of tuberculosis in adolescence and early life. *Br Med J* 1966;1:413-427.

19. Great Britain Medical Research Council: BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early life. *Br Med J* 1959;2:379-396.

20. Great Britain Medical Research Council: BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early life. *Br Med J* 1963;1:973-979.

21. Great Britain Medical Research Council: BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early life. *Bull WHO* 1972;46:371-385.

22. Hart PD'A, Sutherland I: BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early life. *Br Med J* 1977;2:293-295.

23. Frimodt-Møller J: A community-wide tuberculosis study in a South Indian rural population 1950-1955. *Bull WHO* 1960;22:61-170.

24. Frimodt-Møller J, Thomas J, Parthasarathy R: Observations on the protective effect of BCG vaccination in a South Indian rural population. *Bull WHO* 1964;30:545-574.

25. Frimodt-Møller J, Acharyulu G, Parthasarathy R: Observations on the protective effect of BCG vaccination in a South Indian rural population: Third report. *Indian J Tuberc* 1969;15:40-51.

26. Frimodt-Møller J, Acharyulu G, Pillai K: Observations on the protective effect of BCG vaccination in a South Indian rural population: Fourth report. *Bull Int Union Tuberc* 1973; 48:40-52.

27. Tuberculosis Prevention Trial, Madras: Trial of BCG vaccine in South India for tuberculosis prevention. *Indian J Med Res* 1979;70:349-363.

28. Tuberculosis Prevention Trial, Madras: Trial of BCG vaccine in South India. *Indian J Med Res* 1980;72(suppl):1-74.

29. Springett V: The value of BCG vaccination. *Tubercle* 1965;46:76-84.

30. Hart PD'A. Efficacy and applicability of mass BCG vaccination in tuberculosis control. *Br Med J* 1967;1:587-592.

31. Sutherland I: State of the art in immunoprophylaxis in tuberculosis, in Chamberlayne EC (ed): *Status of Immunization in Tuberculosis: Fogarty International Center Proceedings No. 14*, publication (NIH) 72-68. US Dept of Health, Education, and Welfare, 1971, pp 113-125.

32. Tendam H, Toman K, Hitze K, et al: Present knowledge of immunization against tuberculosis. *Bull WHO* 1976;54:255-269.

33. Eickhoff T: The current status of BCG immunization against tuberculosis. *Annu Rev Med* 1977;28:411-423.

34. BCG: Bad news from India. *Lancet* 1980; 1:73-74.

35. Greenwood M: *Epidemics and Crowd-Diseases*. London, Williams and Norgate Ltd, 1935, pp 78-97.

36. Vaccination against tuberculosis, report of an ICMR/WHO scientific group. *WHO Tech Rep Ser*, 1980, pp 1-21.

37. Dubos R: Acquired immunity to tuberculosis. *Am Rev Respir Dis* 1964;90:505-515.

38. Palmer C, Long M: Effects of infection with atypical mycobacteria on BCG vaccination and tuberculosis. *Am Rev Respir Dis* 1966; 94:553-568.

39. Gifford R, Feinstein A: A critique of methodology in studies of anticoagulant therapy for acute myocardial infarction. *N Engl J Med* 1969;280:351-357.

40. Sackett D, Gent M: Controversy in counting and attributing events in clinical trials. *N Engl J Med* 1979;300:1410-1412.

41. Farer LS: Mycobacterium tuberculosis: Bacteriology, epidemiology and treatment, in Mandel G, Douglas R, Bennett J (eds): *Principles and Practice of Infectious Diseases*. New York, John Wiley & Sons Inc, 1979, pp 1905-1924.

42. Armitage P: *Statistical Methods in Medical Research*. New York, John Wiley & Sons Inc, 1971, p 97.

43. Walter S: The distribution of Levin's measure of attributable risk. *Biometrika* 1975;62:371-374.

44. Comstock G, Sartwell P: Tuberculosis studies in Muscogee County, Georgia: IV. Evaluation of a community-wide x-ray survey on the basis of six years of observations. *Am J Hyg* 1955;61:261-285.

45. Smith DT: Isoniazid prophylaxis and BCG vaccination in the control of tuberculosis. *Arch Environ Health* 1971;23:235-242.

George Bass was born at Aswarby in Lincolnshire on Jan 30, 1771. After his father's death, his mother left the farm and moved a short distance to Boston; at this port on the river Witham, Bass was introduced to ships.

His mother apprenticed him to a local surgeon apothecary, Patrick Francis. For two years he learned how to cup and blister, perform venesection, and set fractured bones and to make up the complicated prescriptions of the day. He then went to London, where he obtained his Membership of the Company of Surgeons on April 2, 1789. Bass wrote to his mother that he "could never submit to the fiddle faddle and necessary quackery of practice" and "after all probably not paid, and when paid, paid like a prostitute with my compliments."

Two months later he qualified as "a surgeon's mate—any rate." Within a week he was at sea in the English Channel on the *H. M. S. Flirt*, an unrated 14-gun ship with 73 men aboard. He was then transferred to the *H. M. S. Gorgon*, which was to search for the mutineers of the *Bounty* and then to join an expedition to the northwest coast of America under the command of Captain Vancouver. He did not sail on the *Gorgon*, however, because of being promoted and assigned to serve on other ships in the war with France. In 1794, he was transferred to a ship bound for New Holland, as Australia then was called. In a small boat named *Tom Thumb*, Bass and Matthew Flinders explored George's River, which flows into Botany Bay. Bass made several inland explorations but was unable to cross the Blue Mountains west of Sydney.

His greatest feat was an 11-week voyage in a whale boat during which he demonstrated the existence of Bass Strait and discovered Twofold Bay, Wilson's Promontory, Western Port Bay, and the Shoalhaven River. It was said that the voyage "expressly undertaken for discovery in an open boat, and in which 600 miles of coast, mostly in a boisterous climate, was explored, has not, perhaps, its equal in the annals of maritime history." Bass made many observations of the plants, birds, and animals of the areas where he visited. He described the anatomy of the wombat, the nesting behavior of the albatross, and the venom of several snakes. He also made a number of observations on the Tasmanian aboriginals. In 1797-1798, Bass and Flinders circumnavigated Tasmania.

Bass's health deteriorated and he returned to England, mapping the Straits of Singapore while on his way. He married Elizabeth Waterhouse and three months later sailed on the *Venus* for Port Jackson, Australia, where he planned to sell supplies. Unfortunately, no market existed; but he recouped some of his losses by obtaining pork and salt from the Pacific Islands for the governor at Port Jackson.

Bass then planned to sail to the South American coast and wrote to his brother-in-law, Henry Waterhouse, that his voyage "combined circumstances of a different nature also." He said, "If our approaching voyage proves at all fortunate in its issue, I expect to make a handsome thing of it." Perhaps he hoped to smuggle his unsold London cargo to South America and make a great profit—it is not known. In any event, he sailed from Port Jackson on Feb 5, 1803, and was never heard of again. Some thought that he was captured by the Spaniards and sent to the mines of Peru or Chile. However, there is no record of a ship named *Venus* reaching the South American coast during this time. Bass may well have been shipwrecked off the South Island of New Zealand, where a number of unidentified wrecks have been found.

He was honored by a stamp issued by Australia in 1966.—ROBERT A. KYLE, MD, MARC A. SHAMPO, PHD

Bulletin of the World Health Organization, 58 (1): 37-41 (1980)

(5)

Does BCG vaccination protect the newborn and young infants?*

H. G. TEN DAM[1] & K. L. HITZE[2]

In recent years, BCG vaccination has been applied to the newborn in many immunization programmes at the time of the changeover from mass vaccination to an integrated programme. Whereas the efficacy of BCG vaccination in adolescents and adults has been studied in a number of controlled trials, there is very little direct evidence of the efficacy of BCG vaccination against infant tuberculosis. This article reviews the evidence that is available concerning vaccination of the newborn from both controlled trials and retrospective studies. Further controlled prospective studies and epidemiological surveillance of BCG vaccination in infancy are highly indicated.

During the last few decades, BCG vaccination has been applied on an ever-increasing scale. Campaigns have usually been initiated with an extensive mass campaign to cover the eligible population in a short time, and this has been followed by a programme integrated with the general health services to keep up with the birth rate and thus maintain and possibly increase the coverage obtained. In many of the maintenance programmes, vaccination is therefore directed to the youngest age groups—including the newborn.

Among the advantages of this strategy are that all children are vaccinated before being exposed to infection and that protection is afforded against the serious forms of childhood tuberculosis—miliary tuberculosis and tuberculous meningitis—which are still often fatal, even when chemotherapy is available. On the other hand it is generally considered that a single vaccination at birth does not give protection for life, and that revaccination is necessary at school age.

Although vaccination with BCG is now being applied to the newborn, there is very little direct evidence concerning the degree of protection afforded to very young infants. Most of the evidence of the efficacy of BCG vaccination comes from clinical observations in adolescents and young adults, and much of it has been contradictory. Several studies have been reviewed recently, and the reasons for the differences in protection remain unknown.[a,b]

Experience has, in fact, shown that the response to BCG vaccination in the newborn is not necessarily the same as in adolescents and young adults, since the immediate response to BCG and the clinical types of tuberculosis in the two age groups are different. A dose of BCG that is well tolerated in schoolchildren often causes suppurative lymphadenitis in a high proportion of the newborn. Whereas this, unlike the local reaction at the site of vaccination, could be taken to indicate a good "take" of the vaccination, the resulting post-vaccination tuberculin sensitivity in the newborn invariably appears to be lower than in older children given the same dose of BCG. This indicates that the immunological response is relatively low, and thus that protection may be less. Moreover, in order to avoid an

* A French version of this article will appear in a later issue of the *Bulletin*.

[1] Scientist, Tuberculosis and Respiratory Infections, Division of Communicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

[2] Chief Medical Officer, Tuberculosis and Respiratory Infections, WHO, Geneva.

[a] TEN DAM, H. G. ET AL. *Bulletin of the World Health Organization*, 54: 255 (1976).

[b] TUBERCULOSIS PREVENTION TRIAL. *Bulletin of the World Health Organization*, 57: 819 (1979).

unacceptably high incidence of suppurative lymphadenitis in programmes directed specifically to the lowest age group, the dose of BCG vaccine is usually reduced, and this results in a further decrease of the immunological response as evidenced by the post-vaccination tuberculin sensitivity.

This article reviews the evidence from three controlled trials that have involved the vaccination of the newborn, all carried out in the 1930s, and also the only recent evidence that is available on this question which comes from retrospective studies.

CONTROLLED TRIALS IN THE NEWBORN

The first attempt to examine the efficacy of BCG vaccination of young infants in a controlled trial was started in 1926 in New York City.[c] Up to 1933, half of the infants (under 1 year old, many under 4 weeks) referred from tuberculous homes were vaccinated, the others serving as controls. During this period the results were extremely favourable: there were 3 deaths from tuberculosis among 445 vaccinated children but 18 deaths among 545 controls. However, the allocation to the vaccinated group and the control group was not at random but by selection, and it was realized that this could have biased the result. From 1933 onwards, therefore, infants were allocated to the vaccination and control groups alternately. From then on, the efficacy of BCG vaccination appeared to diminish: up to 1944, 8 children died from tuberculosis among the 566 who were vaccinated, and 8 died among the 528 controls. However, in the control group 49 were lost to follow-up, whereas in the vaccinated group only 29 children were lost; this significant difference could have biased the result. Also, in this trial, the BCG strain became contaminated in 1932 and it is possible that the strain was modified during the back-selection process. Another point worth mentioning is that, contrary to Calmette's recommendations and to the practice in later trials, the infants were not systematically isolated before and after vaccination. Some children, therefore, may have been infected before immunity could develop. Among the children who were fortuitously isolated, there were 3 deaths among 96 controls and only 1 death among 91 vaccinated children.

In 1933, Ferguson & Simes started a controlled trial in Saskatchewan Indians.[d] Infants were vaccinated intradermally (21 orally) within 10 days of birth. The intake lasted until the end of 1945. Allocation to the vaccinated and the control groups was by paired families with annual rotation. According to the authors, this procedure resulted in balanced groups of 306 vaccinated children and 303 controls: the general mortality in the first year of life was 12.7% among those vaccinated and 12.5% among the controls. During the 14 years of the study there were 53 deaths among those vaccinated with BCG and 63 among the controls. Among the 306 vaccinated children, there were 6 cases of tuberculosis, 2 of whom died. Among the 303 controls, there were 29 cases, 9 of whom died. Thus the degree of protection observed was over 80%.

A study of BCG vaccination of the newborn by a percutaneous multiple puncture method was started by Rosenthal et al. in 1937.[e] It comprised 3381 infants of whom about half were vaccinated during the first week after birth if the household members were free from tuberculosis. (Vaccinated infants were also included in some instances when a household member was at first suspected of having tuberculosis but within 3 months showed a cleared X-ray picture.) The statistical analysis presented by the authors showed that the two groups were not entirely comparable, since there was an excess of follow-up among the vaccinated subjects under 2 years of age and among the control subjects over 2 years of age. The

[c] LEVINE, M. I. *Pediatrics*, 15: 288 (1949).
[d] FERGUSON, R. G. & SIMES, A. B. *Tubercle*, 30: 5 (1949).
[e] ROSENTHAL, S. R. ET AL. *Pediatrics*, 28: 622 (1961).

investigators considered that these differences should not have influenced the observed morbidity and mortality data, a viewpoint they substantiated by showing that the morbidity from measles, whooping cough, and other childhood diseases was the same in both groups. As regards tuberculosis, however, the difference in morbidity was highly significant: there were 17 cases (including 1 death) among the 1716 vaccinated and 65 cases (including 6 deaths) among the 1665 controls—75% protection.

RETROSPECTIVE STUDIES

Retrospective studies are well known to be subject to observer bias, an important aspect of which is that investigators often set out to prove a certain concept and accordingly select their material. The use of modern electronic data processing equipment greatly facilitates such a biased selection, since large amounts of data can be made available easily and many "hypotheses" can be tested or even formulated after inspection of the material. Another form of bias stems from a preference to report success rather than failure. Retrospective studies, therefore, are best considered to attain validity only if they are confirmed repeatedly.

Mortality and morbidity statistics are frequently used to show the impact of a certain health measure. However, such data should be interpreted with caution since a statistical association between the application of a health measure and morbidity or mortality does not necessarily indicate cause and effect; both events may, for example, be associated with another factor. This no doubt applies in tuberculosis epidemiology. In European countries, for which fairly reliable statistics are available, there has been a steady decline in tuberculosis morbidity and mortality since the beginning of the century. This decline is often referred to as "natural" or is explained as a result of better living conditions; it could also result, at least partly, from the practice of isolating tuberculosis patients in sanatoria and thus eliminating the sources of infection. Be this as it may, it would clearly be incorrect to attribute the decline in morbidity to the (often simultaneous) introduction of chemotherapy and BCG vaccination. While the introduction of BCG vaccination of the newborn might have a pronounced effect on the incidence of infant tuberculosis, the impact of effective case-finding and treatment would also be most noticeable in this age group. For this reason, reports that merely show a decline in infant tuberculosis after the introduction of BCG vaccination are not considered here.

An interesting analysis of morbidity statistics for different countries was made by Bjartveit & Waaler, who studied the association between the decline of tuberculosis in various age groups and the age at which vaccination was given.[5] This association was quite pronounced and thus provided evidence of the efficacy of BCG vaccination. In one of the countries included in the analysis, BCG was given to the newborn, and the conclusions as regards efficacy would appear to apply to BCG vaccination of this age group. Ehrengut compared the decline of the mortality from tuberculous meningitis and miliary tuberculosis in Hamburg, where BCG vaccination had been given to the newborn since 1953, with that in Bavaria where there has been no such vaccination programme.[6] In Hamburg the decline was much faster, and during the period 1961–70 there was only 1 death in comparison with the 65 deaths recorded in Bavaria.

In May 1975, BCG vaccination was suspended in the Federal Republic of Germany because a new vaccine had given rise to untoward reactions. Whereas in 1973 and 1974, the official statistics showed that the incidence of tuberculosis in the 0–1-year age group was 35

[5] BJARTVEIT, K. & WAALER, H. *Bulletin of the World Health Organization*, 33: 289 (1965).

[6] EHRENGUT, W. *Padiatrische Fortbildungkurse für die Praxis*, 11: 529 (1972).

and 33, respectively, 79 cases were observed between 1 September 1975 and 1 Septe
1976.[h] In this case, the causal relationship seems to be beyond doubt, but as the da
1975–76 were collected by questionnaire the comparability may be questioned.

In retrospective studies comparison with a control group from the same populatio
sometimes possible, the best available control group being generally those who refu
vaccination. Although in these cases the vaccinated and unvaccinated groups are n
selected, their comparability may be quite good, especially if the groups do not repre
extremely large or small proportions of the eligible population. The comparability may
verified from exposure to tuberculosis, incidence of other diseases and disorders, accide
etc. Some doubts with regard to comparability may nevertheless remain, and the value
the observations, therefore, depends largely on the magnitude of any difference obser
between the groups. Statistical significance tests should be used with caution, and
protective effect of the vaccination is generally difficult to estimate. Some examples
studies of this kind are given below.

Among the children who resided in the City of Manchester and were born in the per
1951–60, 25 478 were born in a certain group of hospitals. BCG vaccination was offered
all these newborns, and was accepted for 10 326. Subsequently, from clinical records, it w
found that of the children in the area who had tuberculosis during this period, 40 had be
born in the hospitals of this group. All 40 cases appeared to have occurred in the 15 1
unvaccinated children.[i] Self-selection cannot reasonably be invoked to explain t
difference in incidence. During the observation period the vaccination coverage increas
whereas the risk of tuberculosis decreased. Simple comparison of those vaccinated w
those not vaccinated would produce a spurious beneficial effect of the vaccination,
obviously not of the extent observed.

The results have recently been published[j] of a retrospective study that concerned 6
infants who were vaccinated at birth, in Hamburg in 1954, and 9524 who were not. Up
1971, 9 of the vaccinated and 130 of the unvaccinated children had developed tuberculo
Of the 30 370 children born in 1963, 27 371 were vaccinated and 2 999 were not. There w
11 cases of tuberculosis among the vaccinated and 16 cases among the unvaccina
children over the 8-year follow-up period. It is interesting to note that the secular trend
tuberculosis morbidity between 1954 and 1963 in the vaccinated and the unvaccina
children was similar. This would have been expected if exposure to tuberculosis infec
had been the same in the two groups.

In 1965–67 in China (Province of Taiwan), 109 cases of tuberculous meningitis w
observed in the 0–5-year age group. Only 4 cases out of the 109 had a BCG scar, whe
34% of all the children had been vaccinated.[k]

In Hong Kong, between July 1971 and September 1974, there were 159 cases of confir
tuberculosis in children born after July 1966, among which were 42 cases of meningitis
23 of miliary tuberculosis. Of these, 150 were in the vaccinated and only 9 in the unva
nated children. Nevertheless, as the vaccination coverage was very high, the average ann
incidence was 1.0 and 1.7 per 10 000 children respectively.[l] The comparability of the t
groups is open to some doubt since the unvaccinated group was very small in compari
with the vaccinated group.

---

[h] GENZ, H. *Deutsches medizinische Wochenschrift*, 102: 1271 (1977).

[i] GRIFFITH, M. I. In: *Transactions of the Sixth Commonwealth Conference of Chest and Heart Association, London, h*
London, 1962, p. 47.

[j] EHRENGUT, W. & STELLMER, H. *Immunität und Infektion*, 5: 35 (1977).

[k] GRZYBOWSKI, S. In: *Immunization in tuberculosis*, Bethesda, 1971, p. 133 (DHEW Publication No. [NIH] 72-68).

[l] ALLAN, W. G. L. *Bulletin of the International Union against Tuberculosis*, 51: 239 (1976).

DISCUSSION

Taken at face value, the evidence presented above suggests that BCG vaccination of the newborn confers considerable protection against tuberculosis in infants and young children. On the other hand it should be realized that the evidence is both scanty and superficial. Thus, the fact that no study clearly showed a disappointing result, as has happened for vaccination of adolescents, may well be due to the insufficient number of studies undertaken or reported. Moreover, the actual degree of protection afforded by the variety of BCG products used cannot be determined accurately, and most of these products are no longer available and cannot be reproduced.

The studies mentioned refer mainly to vaccination during the first few days after birth. The strategy introduced recently in expanded immunization programmes, however, is to give BCG vaccination a few months after birth and the implications of this different timing with regard to the incidence of suppurative lymphadenitis and the degree of post-vaccination tuberculin sensitivity are currently being studied.

As regards protection, it may be reassuring to note that BCG vaccination invariably appeared effective in those studies in which tuberculosis disease appeared to occur relatively soon after infection, a situation that applies *ipso facto* in infant tuberculosis. Epidemiological factors that could impair the effect of BCG vaccination in adolescents, such as sensitization with atypical mycobacteria and repeated infection, are less likely to play a role in young infants. Nevertheless it is highly desirable that both controlled prospective studies and, where possible, epidemiological evaluation should be initiated as soon as possible.

A Case-Control Study to Evaluate the Effectiveness of Mass Neonatal BCG Vaccination among Canadian Indians

T. KUE YOUNG, MD, MSc, AND EARL S. HERSHFIELD, MD

Abstract: This paper reports a case-control study to assess the protective effect of BCG (bacille Calmette-Guérin) vaccination among Indian infants in Manitoba, Canada. A record of past BCG vaccination was found in 49 per cent of the tuberculosis cases, compared to 77 per cent of the controls, yielding a relative risk of 0.30. Stratified analysis, controlling for age, increased the relative risk to 0.39 (95% confidence interval 0.22 – 0.69). The preventive fraction was 44 per cent. Non-differential misclassification of exposure status could have occurred; if this was adjusted for, the relative risk would be reduced. If only bacteriologically confirmed cases were analyzed, the age-adjusted relative risk was 0.27. The protective effect of BCG vaccination in the newborn among Manitoba Indians is therefore at least 60 per cent. The implications for health policy in this population are further discussed. (*Am J Public Health* 1986; 76:783–786.)

Introduction

BCG (bacille Calmette-Guérin) vaccination to control tuberculosis is widely practiced around the world, but conflicting results from several large-scale trials have cast doubt on its effectiveness.[1–3] Despite the disappointing results of the latest trial in Madras, India,[4] expert committees of the World Health Organization continue to recommend the mass use of BCG vaccination in developing countries, and stress the need for further research.[5–7]

In Canada, Indian and Inuit (Eskimo) newborns are one of the few high-risk groups which still receive BCG routinely. This policy of the federal Medical Services has been in force at least since the mid–1960s. The use of BCG on a mass scale in this population is still recommended by the most recent edition of the Canadian Tuberculosis Standards published by the national lung association.[8] In Manitoba, freeze-dried BCG manufactured by Connaught Laboratories is used. The dose for infants is 0.05 mg (half the adult dose) administered intradermally.

Raj Narain, former Director of the Madras Tuberculosis Prevention Trial, advocated the conduct of a randomized controlled trial of BCG vaccination among Canadian Indians and Inuit in 1982.[9] An alternative, suggested by Smith, was a case-control study.[10]

In this paper, we report a case-control study to determine the effectiveness of BCG vaccination of newborns in preventing the development of tuberculosis among Indians in Manitoba.

Methods

Selection of Cases

Cases of new active tuberculosis diagnosed between 1979 and 1983 among Registered Indians living on Indian Reserves were obtained from the Manitoba Tuberculosis Registry in Winnipeg. Notification of tuberculosis is required by law; treatment services for this disease, while no longer sanatorium-based, are centralized in one facility in this province. The Provincial Tuberculosis Control Services contracts with the federal Medical Services Branch to provide diagnostic, treatment, and follow-up services for all Indian tuberculosis patients. There is thus a high degree of completeness in the ascertainment of cases for the population studied.

Cases were restricted to those born on or after January 1, 1965—those most likely to have benefited from the mass BCG program and most likely to have adequate records. Only childhood cases (under the age of 15 at the time of diagnosis) were considered. These cases from a population-based registry were therefore all incident, rather than prevalent, cases.

No attempt was made to validate the diagnostic accuracy of the cases in the Registry, but separate analyses were made for all registered cases, and for cases which were bacteriologically confirmed.

A total of 71 cases were selected. All records and immunization cards were reviewed and abstracts prepared by the principal investigator during visits to all facilities. Fifty cases were classified as primary, 11 pulmonary, five pleurisy, two miliary, two lymph nodes, and one disseminated. No meningitis case occurred during the period studied.

Selection of Controls

Controls were randomly selected from the general Registered Indian population in the same communities which contributed tuberculosis cases, with the same age restriction. Matching on an individual basis was not performed; the problem of potential confounding was handled by stratified analysis. Three times as many controls as cases were selected.

The controls were all living and never had active tuberculosis up to the time of the investigator's site visit. As they were selected from a listing of the communities' residents, they were representative of the general population at risk.

All records and immunization cards were reviewed and abstracts prepared by the principal investigator during visits to the health facilities.

The ages of individuals when vaccinated were not consistently recorded. However, the official policy had always been to give BCG at birth prior to discharge from hospital. Infants who were missed at birth (for a variety of reasons such as lack of cooperation or enthusiasm of some local hospitals) were "caught up" by public health nurses during regular well-child clinics.

Statistical Analysis

The measure of association between past BCG vaccination and development of new active tuberculosis is the odds ratio which provides an estimate of the relative risk (R). For

Address reprint requests to T. Kue Young, MD, MSc, FRCP(C), Assistant Professor, Department of Social and Preventive Medicine and the Division of Community and Northern Medicine, Faculty of Medicine, University of Manitoba, 750 Bannatyne Avenue, Winnipeg, Manitoba, Canada R3E 0W3. Dr. Hershfield, FRCP(C), is Director, Respiratory Hospital, Health Sciences Center, and Professor, Department of Medicine, University of Manitoba. This paper, submitted to the Journal August 15, 1985, was revised and accepted for publication October 28, 1985.

© 1986 American Journal of Public Health 0090-0036/86$1.50

TABLE 1—Comparison of Cases and Controls with regard to Age, Sex, and Past Isoniazid Use

Variables		Cases		Controls	
		No.	%	No.	%
Sex	Male	40	56.3	103	48.4
	Female	31	43.7	110	51.6
Year of Birth	1965–69	19	26.8	34	16.0
	1970–74	33	46.5	59	27.7
	1965–74	52	73.3	93	43.7
	1975–79	13	18.3	69	32.4
	1980–83	6	8.5	51	23.9
	1975–83	19	26.8	120	56.3
Past Isoniazid Use	Yes	4	5.6	7	3.3
	No	67	94.4	206	96.7

BCG to be effective in preventing tuberculosis, R should be less than 1. The protective effect of BCG is then 100 (1–R) per cent.

Disease status and exposure status were dichotomized into "case" or "control", and "BCG" or "non-BCG", respectively. Stratified analyses of a series of 2×2 contingency tables were performed according to the methods described by Mantel and Haenszel[11] and Miettinen[12] which gave summary estimates of relative risks across all strata as well as their 95 per cent confidence intervals. Computations were facilitated by the use of the HP-41CV programmable calculator and the published programs by Rothman and Boice.[13]

Variables to be controlled for include age (year of birth), sex, locality ("northern, remote" vs "southern, road-accessible"), and history of past isoniazid prophylaxis. Past use of isoniazid is not strictly a potential confounder, since it is not associated with the exposure in question, although it is expected to affect the incidence of disease. Past prophylaxis may have a possible interactive effect with vaccination in that a person who has received both BCG and isoniazid may have a much reduced chance of developing tuberculosis. On the other hand, a person who receives isoniazid prophylaxis is usually at higher risk for the disease because of close contact with an active case.

Results

Overall, 49.3 per cent of cases had a record of past BCG vaccination, compared to 76.5 per cent of controls. The crude (unadjusted) relative risk was 0.30 (95% confidence interval 0.17 to 0.52).

Table 1 compares cases and controls with regard to age distribution, sex, and past usage of isoniazid. Older cases and controls tend to have a lower vaccination coverage than those born more recently. Since the sampling was stratified by community, the distribution of locality types was identical in both cases and controls.

Table 2 indicates that age adjustment alone increased the overall relative risk from 0.30 to 0.39 (95% confidence interval 0.22 to 0.69). Whether two strata (year of birth 1965–74, and 1975–83) or four strata (1965–69, 1970–74, 1975–79, and 1980–83) were used in the calculation had little effect on the adjusted relative risk. Subsequent analyses will therefore only adjust for year of birth based on two strata.

To investigate the possibility that some of the "cases" recorded in the Tuberculosis Registry were not in fact true cases, the analysis was repeated using only bacteriologically confirmed cases. These 37 cases had some type of body specimen (sputum, gastric aspirate, cerebrospinal fluid, urine, lymph node discharge, etc.,) positive on either smear or culture. The age-adjusted relative risk was now 0.27 (95% confidence interval 0.13 to 0.56) (Table 3).

Misclassification of exposure status was also a possibility since the study depended on the quality of existing health service records. Over the years, records were handled by numerous health workers. If a person did not receive BCG, it seems unlikely that it would be recorded as having been given; more likely, a person may have received BCG without a record having been made. It is reasonable to assume that any misclassification that did occur would be of the "non-differential" type, i.e., cases and controls were equally likely to have their vaccination status recorded incorrectly to the same degree. Under this set of assumptions, correcting for

TABLE 2—Stratified Analyses of the Association between BCG Vaccination and Tuberculosis

Variable Adjusted	Strata	Cases		Controls			
		No.	% BCG	No.	% BCG	RR^{mh}	95% Confidence Interval
nil	—	71	49.3	213	76.5	0.30	0.17–0.52
Year of Birth	1965–69	19	47.4	34	58.8		
	1970–74	33	42.4	59	67.8		
	1975–79	13	61.5	69	82.6		
	1980–83	6	66.7	51	90.2	0.40	0.22–0.70
	1965–74	52	44.2	93	64.5		
	1975–83	19	63.2	120	85.8	0.39	0.22–0.69
Sex	Male	40	55.0	103	73.8		
	Female	31	41.9	110	79.1	0.30	0.18–0.52
Past Isoniazid Use	Yes	4	25.0	7	85.7		
	No	67	50.8	206	76.2	0.30	0.17–0.52
Locale	North	31	74.2	93	86.2		
	South	40	30.0	120	67.5	0.26	0.14–0.46
	21 individual communities					0.23	0.12–0.43
Year of Birth and Sex	(4 strata)					0.39	0.22–0.70
Year of Birth and Location	(4 strata)					0.35	0.19–0.66
Sex and Location	(4 strata)					0.26	0.15–0.47
Year of Birth and Sex and Isoniazid Use	(8 strata)					0.40	0.23–0.70

Notes: RR_{mh} = Mantel-Haenszel summary estimate of relative risk.

TABLE 3—Selected Analyses Using Only Bacteriologically Confirmed Cases

Variable Adjusted	Strata	Cases		Controls		RR_{mh}	95% Confidence Interval
		No.	% BCG	No.	% BCG		
nil	—	37	40.5	213	76.5	0.21	0.11–0.42
Year of Birth	1965–74	27	33.3	93	64.5		
	1975–83	10	60.0	120	85.8	0.27	0.13–0.56
Sex	M	21	38.1	103	73.8		
	F	16	43.8	110	79.1	0.21	0.11–0.43
Past Isoniazid Use	Yes	1	0	7	85.7		
	No	36	41.7	206	76.2	0.21	0.11–0.42
Year of Birth and Sex Combined	1965–74 M	15	26.7	50	66.0		
	1965–74 F	12	41.7	43	62.8		
	1975–83 M	6	66.7	53	81.1		
	1975–83 F	4	50.0	67	89.6	0.27	0.13–0.58

misclassification would have resulted in an even smaller relative risk (i.e., higher protective effect). (The mathematical computations to demonstrate the effect of misclassification on the relative risk are available from the author upon request.)

The proportion of potential new cases that were prevented, the "prevented fraction" (PF),[14] is determined by:

$$PF = Pc\,(1-R)/[Pc\,(1-R)+R]$$

where Pc is the estimated proportion of cases that are vaccinated. In this study, Pc = 0.493 and R = 0.39. PF is therefore 0.44, i.e., the vaccination program prevented 44 of every 100 cases that would have occurred in its absence.

According to the 1981 Census of Canada there were 12,195 residents of Indian Reserves in Manitoba aged 0–14 years. The average annual incidence rate of new active tuberculosis for this age group was 136/100,000. Given the relative risk of 0.39, and the proportion of the population who were vaccinated (estimated by the proportions of controls vaccinated) or 0.765, the incidence rate, of tuberculosis among the non-vaccinated was 0.00136/(0.39) (0.765)+(1–0.765), or 0.00255 according to Schlesselman's formula.[15]

The incidence rate among the vaccinated was (0.39) (0.00255), or 0.00099. The risk difference was therefore 0.00255–0.00099, or 0.00156. Thus the average number of cases yearly arising in the Manitoba Indian child population residing in Indian Reserves which can be attributed to non-vaccination (the attributable risk) is (0.00156) (12195) or 19 cases.

Discussion

This study demonstrated that BCG vaccination of newborn Indians in Manitoba offers some protection from the development of tuberculosis in childhood. The protection is not complete: those who received BCG at birth had about 40 per cent of the risk of developing the disease compared to those who did not. The protective effect is thus about 60 per cent.

The only randomized trial of BCG among Canadian Indian newborns was that reported by Ferguson and Sime in Saskatchewan in the 1940s,[16] who demonstrated a protective effect of 80 per cent. During the same period, a trial involving Chicago infants also showed a high degree of protection.[17] There are as yet no case-control studies of the effectiveness of neonatal BCG,[18,19] although a retrospective cohort design used by a group in Manchester[20] demonstrated a protective effect of 75 per cent. Our study, if only bacteriologically confirmed cases were used and if there were no misclassification of BCG status, would also yield a protective effect of over 70 per cent.

There is a possibility that among the controls there may have been undiagnosed cases of tuberculosis. Since only 213 out of over 12,000 eligible individuals, less than 2 per cent, were selected as controls, the probability of selecting an individual who happens to have early undiagnosed tuberculosis is very small, even though the incidence of the disease is high in the Indian population.

Although cases and controls were derived from the same group of communities, we did not adjust for the socioeconomic status of individuals. A satisfactory valid indicator of socioeconomic status among Indians which is sufficiently refined to discriminate between individuals who collectively occupy the low end of most conventional measures has not been adequately developed in Canada. However, one could consider the controls in this study as roughly equivalent to "neighborhood" controls.

Whether 60 per cent protective effect is enough to justify the use of neonatal BCG on a mass scale is a policy issue which cannot be resolved on the basis of this study alone. A cost-benefit analysis, however, can be conducted using some of the data generated in this study. Effectiveness is not the only criterion upon which the decision to launch or continue a mass vaccination program is based. In the Canadian Indian population, the case rate is still some 10 times higher than the Canadian national population. However, the risk of infection (as determined from tuberculin surveys) is not currently known. Tuberculosis epidemiologists prefer the use of the risk of infection rather than the disease or case rate to assess the extent of current transmission of tubercle bacilli in a community.[21,22] In addition, there are other unanswered questions, such as the complication rate from vaccination and the extent of interference of vaccination with case-finding efforts based on the tuberculin test. The decision for the use of BCG vaccination among Indians in Canada is thus considerably more complex than simply resolving the issue of effectiveness.[23]

ACKNOWLEDGMENTS

This study was supported by a grant from the Children's Hospital of Winnipeg Research Foundation. Dr. Young is a recipient of the National Health Research Scholar career award from the Department of National Health and Welfare of Canada (6607-1377-48). Dr. P.G. Smith, Head, Tropical Epidemiology Unit, London School of Hygiene and Tropical Medicine, reviewed the manuscript critically and provided invaluable advice on the statistical analysis. The assistance and cooperation of the many nurses in

thevarious Indian Health Services health centers and nursing stations in Manitoba is gratefully acknowledged.

REFERENCES

1. Ten Dam H, Toman K, Hitze K, *et al*: Present knowledge of immunization against tuberculosis. Bull WHO 1976; 54:255–269.
2. Eickhoff T: The current status of BCG immunization against tuberculosis. Ann Rev Med 1977; 28:411–423.
3. Clemens JD, Chuong, JJH, Feinstein AR: The BCG controversy—a methodological and statistical reappraisal. JAMA 1983; 289:2362–2369.
4. Tuberculosis Prevention Trial: Trial of BCG vaccines in south India for tuberculosis prevention: first report. Bull WHO 1979; 57:819–827.
5. World Health Organization: Vaccination against Tuberculosis. Report of an ICMR/WHO Scientific Group. Tech Rep Ser No 651. Geneva: WHO, 1980.
6. World Health Organization: BCG Vaccination Policies. Report of a WHO Study Group. Tech Rep Ser No 652. Geneva: WHO, 1980.
7. World Health Organization: Tuberculosis Control. Report of a Joint IUAT/WHO Study Group. Tech Rep Ser No 671. Geneva: WHO, 1982.
8. Canadian Lung Association: Canadian Tuberculosis Standards. Ottawa: CLA, 1981.
9. Narain R: Need for a BCG trial in Canada's Native population. Can Med Assoc J 1982; 127:101–102.
10. Smith PG: Retrospective assessment of the effectiveness of BCG vaccination against tuberculosis using the case-control method. Tubercle 1982; 63:23–35.
11. Mantel N, Haenszel W: Statistical aspects of the analysis of data fromretrospective studies of disease. JNCI 1959; 22:719–748.
12. Miettinen OS: Estimability and estimation in case-referent studies. Am J Epidemiol 1976; 103:226–235.
13. Rothman KJ, Boice JD: Epidemiologic Analysis with A Programmable Calculator, 2nd Ed. Boston: Epidemiology Resources Inc, 1983.
14. Miettinen OS: Proportion of diseases caused or prevented by a given exposure trait or intervention. Am J Epidemiol 1974; 99:325–332.
15. Schlesselman JJ: Case Control Studies: Design, Conduct, Analysis. New York: Oxford University Press, 1982.
16. Ferguson RG, Sime AB: BCG vaccination of Indian infants in Saskatchewan. Tubercle 1949; 30:5–11.
17. Rosenthal SR, Loewinsohn E, Graham ML, *et al*: BCG vaccination against tuberculosis in Chicago: a twenty-year study statistically analyzed. Pediatrics 1961; 28:622–644.
18. Anon: BCG vaccination in the newborn. Br Med J 1980; 281:1445–1446.
19. Ten Dam HG, Hitze KL: Does BCG vaccination protect the newborn and young infant? Bull WHO 1980; 58:37–41.
20. Curtis HM, Leck I, Bamford FN: Incidence of childhood tuberculosis after neonatal BCG vaccination. Lancet 1984; 1:145–148.
21. Sutherland I: Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. Adv Tuberc Res 1976; 19:1–63.
22. Styblo K: Recent advances in epidemiological research in tuberculosis. Adv Tuberc Res 1980; 20:1–63.
23. Young TK: BCG vaccination among Canadian Indians and Inuit: the epidemiological bases for policy decision. Can J Public Health 1985; 76:124–129.

New Book Review Journal in Mental Health

A different kind of mental health journal was introduced in March 1986 by the publisher of the *American Journal of Orthopsychiatry*.

READINGS: A Journal of Reviews and Commentary in Mental Health will be the field's only interdisciplinary journal to focus exclusively on book reviews. Featuring essay reviews by the outstanding thinkers in the behavioral sciences, *READINGS* will be an essential forum for the debate of both new ideas and traditional concepts. *READINGS'* Overview section of one-paragraph reviews will cover the new literature quickly and comprehensively. The journal will be highlighted by black-and-white photography.

Issued quarterly, *READINGS* will help the mental health professionals keep current on all book publishing relevant to mental health and human behavior. For more information about *READINGS* and charter subscription rates, contact: Ernest Herman, Editor, 212/354-5770, American Orthopsychiatric Association, Inc., Suite 1616, 19 West 44th St., New York, NY 10036.